Disubstituted Indazoles as Potent Antagonists of the Integrin $\alpha_v\beta_3$

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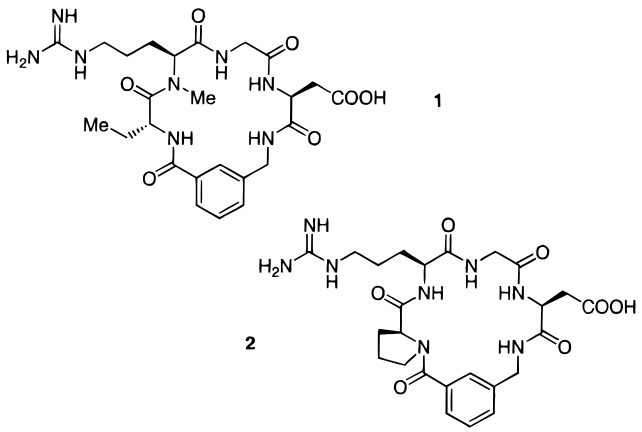
A new series of indazole-containing $\alpha_v\beta_3$ integrin antagonists is described. Starting with lead compound **18a**, variations in a number of structural features were explored with respect to inhibition of the binding of β_3-transfected 293 cells to fibrinogen and to selectivity for $\alpha_v\beta_3$ over GPIIbIIIa, another RGD-binding integrin. Indazoles attached to a 2-aminopyridine or 2-aminoimidazole by a propylene linker at the indazole 1-position and to a diaminopropionate derivative via a 5-carboxylate amide provided the best potency with moderate selectivity. Several differences in the SAR of the diaminopropionate moiety were observed between this series and a series of isoxazoline-based selective GPIIbIIIa antagonists. Compound **34a** (SM256) was a potent antagonist of $\alpha_v\beta_3$ (IC_{50} 2.3 nM) with 9-fold selectivity over GPIIbIIIa.

Introduction

The integrin family of receptors comprises more than 20 heterodimeric cell surface proteins which are involved in cell−cell and cell−matrix adhesion.[1] Integrins are formed by various combinations of at least 16 α-subunits and 8 β-subunits and are very widely distributed in various tissues and cell types. Different integrins have varying affinities and specificities for a multitude of extracellular matrix proteins. The platelet fibrinogen receptor, $\alpha_{IIb}\beta_3$ or GPIIbIIIa, has received an enormous amount of attention over the past decade, since antagonists of GPIIbIIIa have utility in thrombotic disorders such as unstable angina, myocardial infarction, transient ischemic attacks, and perhaps atherosclerosis and stroke.[2]

The classical receptor for vitronectin, the $\alpha_v\beta_3$ integrin, shares a common β-subunit with GPIIbIIIa. While GPIIbIIIa is found almost exclusively on platelets, $\alpha_v\beta_3$ is more widely distributed, occurring on osteoclasts, platelets, endothelial cells, and migrating smooth muscle cells.[3] This integrin has recently attracted significant attention for several possible medical indications. $\alpha_v\beta_3$ is involved in bone resorption by osteoclasts, so antagonists may have utility for the treatment of osteoporosis.[4,5] This receptor plays a major role in angiogenesis and vascular remodeling,[6] suggesting possible applications in combating the growth and metastasis of malignant tumors[7,8] and in suppressing the neovascularization observed in diabetic retinopathy and age-related macular degeneration, two of the leading causes of blindness in adults.[9] Coronary restenosis, a serious complication following angioplasty for the relief of coronary artery occlusion,[10] is reduced by abciximab (ReoPro), a recombinant chimeric antibody which binds to both GPIIbIIIa and $\alpha_v\beta_3$.[11] This benefit is probably due to $\alpha_v\beta_3$ blockade, since selective GPIIbIIIa antagonists were not effective in preventing restenosis.[12,13]

Both GPIIbIIIa and $\alpha_v\beta_3$ bind to extracellular matrix proteins which contain the Arg-Gly-Asp (RGD) sequence. Many cyclic peptide and nonpeptide antagonists of GPIIbIIIa have been reported over the past 10 years. Structural studies of cyclic peptide antagonists have offered some insights into differences in the binding sites. DMP 728 (**1**), which is selective for GPIIbIIIa, exists in a rigid conformation where the RGD portion is extended. A related compound **2** is more flexible but prefers a different conformation, allowing the guanidine and carboxyl groups to approach each other more closely. This change leads to a reversal of selectivity, with **2** binding preferentially to $\alpha_v\beta_3$.[14] A similar effect was seen with a series of cyclic pentapeptides containing the RGD sequence.[15]



A vast literature of nonpeptide GPIIbIIIa antagonists exists.[2] These compounds generally consist of a core scaffold bearing two side chains with basic and acidic groups mimicking the guanidine and carboxylate of the RGD sequence. However, to date only a few nonpeptide antagonists of $\alpha_v\beta_3$ have been reported.[16−20] In our laboratories, structural variation of the potent GPIIbIIIa antagonist prodrug DMP 754 (**3**) yielded a series of isoxazoline-based antagonists derived from **4a**, one of the most potent and selective being **4b**.[21,22] In searching for different scaffolds, exploration of 5,6-bicyclic ring systems bearing appropriate acidic and basic substitu-

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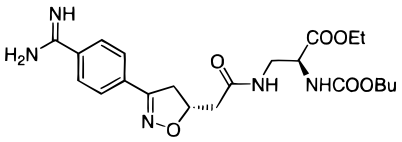
ents yielded **18a** as a lead compound which showed good binding to $\alpha_v\beta_3$. We here report the synthesis and structure−activity relationships of this series of indazole-based $\alpha_v\beta_3$ antagonists.



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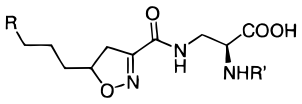
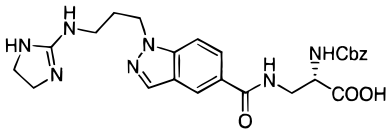


4a (R = $CH_2NHC(=NH)NH_2$, R' = $COOCH_2Ph$)
4b (R = C(=O)NH-2-imidazolyl, R' = SO_2mesityl)

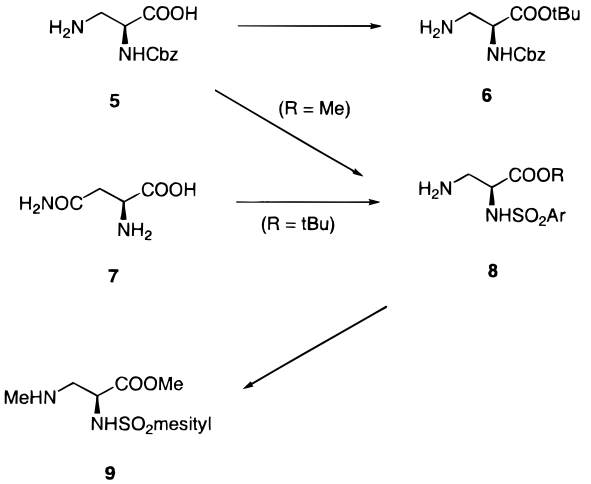


18a

Chemistry

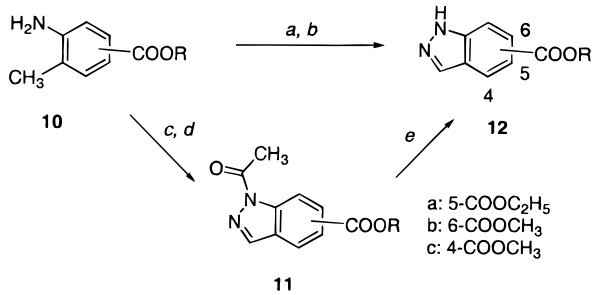
Synthesis of the target compounds was accomplished by attaching the groups bearing the acidic and basic moieties to an indazolecarboxylic acid. Generally, the basic chain was elaborated first on the ester-protected indazolecarboxylate, followed by coupling of the derived acid with an appropriate amine bearing the target compound's carboxylate group, using standard peptide bond-forming methods. The substituted diaminopropionate derivatives used as amine components were prepared using literature methods[23−25] from either the commercially available diaminopropionate derivative **5** or (*S*)-asparagine **7** (Scheme 1). The (*R*)-enantiomer of **6** was prepared from the commercially available (*R*)-isomer of **5**. The *N*-methyl derivative **9** was prepared from **8** (R = Me, Ar = mesityl) using the method of Sakai and Ohfune.[26]

Scheme 1. Preparation of Diaminopropionate Derivatives



Indazole-6-carboxylic acid[27,28] has been reported in the literature, but other isomers were unknown. The esters **12** were prepared from the corresponding aminobenzoate esters **10** using the Jacobson method (diazotization followed by base treatment) as shown in Scheme

Scheme 2. Preparation of Indazolecarboxylate Esters[a]



[a] Reagents: (a) HCl, NH_4BF_4, $NaNO_2$, H_2O, 0 °C; (b) KOAc, $CHCl_3$; (c) Ac_2O, KOAc, $CHCl_3$; (d) nAmONO, 18-crown-6, $CHCl_3$, △; (e) HCl, H_2O, EtOH.

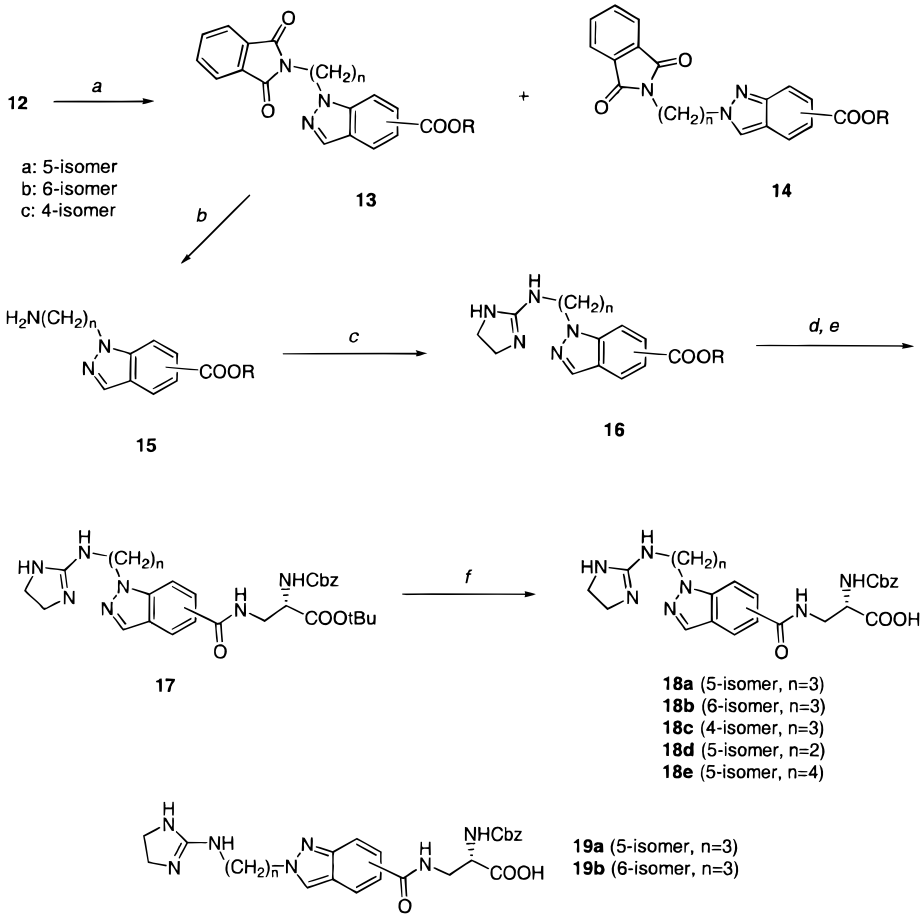
2.[29] For the large-scale preparation of **12a**, the modification of Rüchardt and Hassmann[30] allowed easy purification of the intermediate **11a** by distillation, followed by acid hydrolysis of the acetyl intermediate.

Basic chain attachment was achieved by one of several methods. The approach shown in Scheme 3 allowed variation of both the basic chain length and the positioning of the substituents on the indazole core. Alkylation of the indazole anion with a phthalimide-protected bromoalkylamine provided mixtures (ca. 3:2) of the 1- and 2-alkylated products **13** and **14** in good overall yields. This lack of selectivity for indazole alkylation had been reported previously;[31−33] fortunately the 2-alkylated products could be easily removed by flash chromatography and elaborated separately to isomeric target compounds **19**. Hydrazine removed the phthalimide protecting group of **13** to give the amine **15**, which without purification provided **16** upon reaction with 2-thiomethyl-4,5-dihydroimidazole hydroiodide. The ester was saponified, and the crude carboxylic acid was coupled with **6**, followed by deprotection to the final products **18**. These compounds, as well as the other final products described herein, are amorphous solids which were generally isolated as trifluoroacetate salts following preparative reverse-phase HPLC purification and either lyophilization or ether trituration.

An improved synthesis of the aminopropylindazole intermediate **21** (**15a**, with $n = 3$ and R = Et) is shown in Scheme 4. Conjugate addition of **12a** to acrylonitrile in ethanol with catalytic base provided the nitrile **20**, with no traces of the 2-alkylated isomer detectable, as reported for indazole itself.[34] At early times in the reaction, both isomers were present by TLC, but the undesired isomer disappeared as the reaction progressed. This suggests that the reversible nature of the conjugate addition led to the thermodynamically preferred product **20**, in contrast to the irreversible alkylation shown in Scheme 3 which presumably gave a kinetic mixture. The nitrile was converted to the amine hydrochloride **21** by catalytic reduction in the presence of small amounts of HCl generated in situ from chloroform.[35]

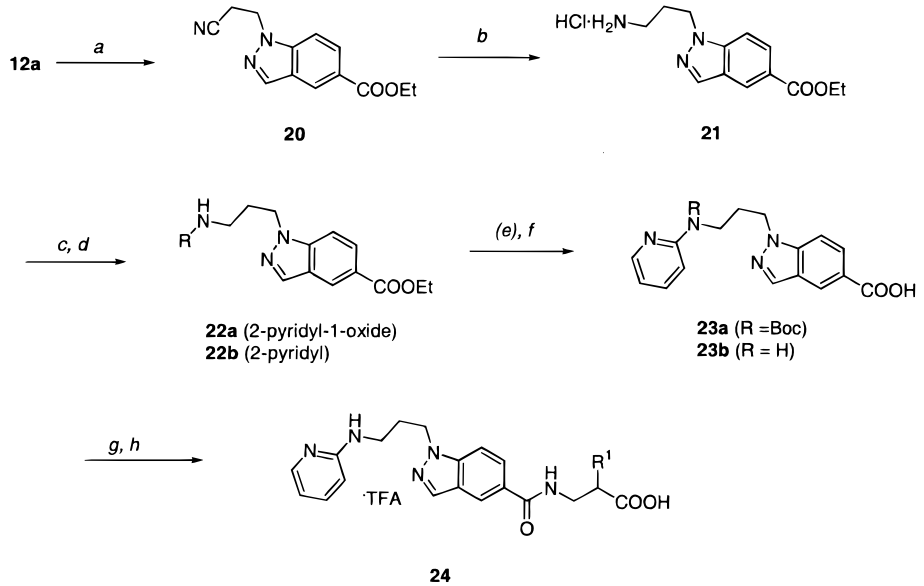
Scheme 4 also illustrates the incorporation of the 2-aminopyridine group as the basic moiety. Compound **21** could not be induced to react with 2-chloropyridine or 2-bromopyridine, but with 2-chloropyridine 1-oxide in the presence of solid sodium bicarbonate[36] the *N*-oxide **22a** was obtained in 80% yield. Reduction of the *N*-oxide was followed by protection of **22b** as the Boc derivative. The ester was saponified, and **23a** was coupled with the

Scheme 3. Initial Synthetic Approach[a]



[a] Reagents: (a) $KN(TMS)_2$, $PhthN(CH_2)_nBr$, THF, △; (b) H_2NNH_2, EtOH; (c) 2-MeS-4,5-dihydroimidazole·HI, pyridine, △; (d) NaOH, H_2O, EtOH, △, HCl, H_2O; (e) **6**, DCC, HOBT, DMF; (f) CF_3COOH, CH_2Cl_2.

Scheme 4. Preparation of Aminopropyl Intermediate **21** and Aminopyridine Derivatives[a]

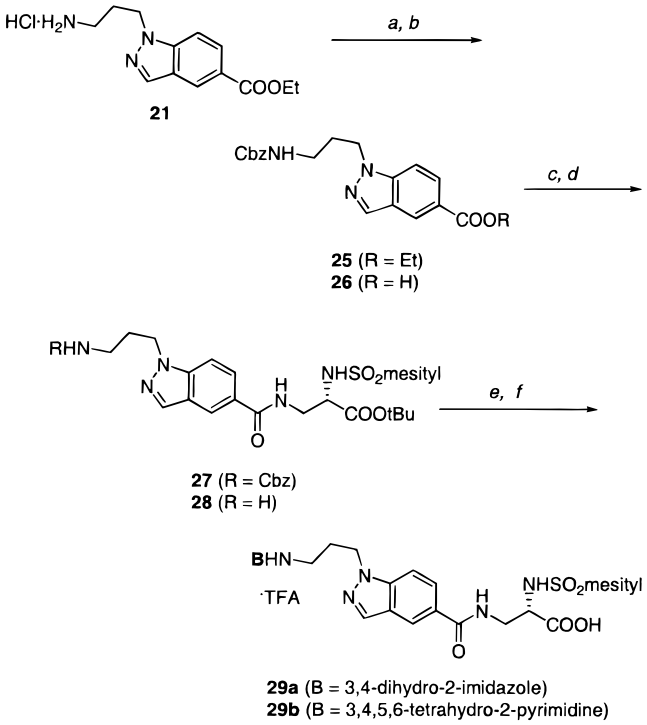


[a] Reagents: (a) $CH_2{=}CHCN$, $NaN(TMS)_2$ (cat.), EtOH, △; (b) H_2, Pd/C, $CHCl_3$, EtOH; (c) 2-chloropyridine 1-oxide, $NaHCO_3$, nBuOH, 100 °C; (d) H_2, Pd/C, EtOH; or $HCOONH_4$, Pd/C, EtOH, △; (e) Boc_2O, DMAP, CH_2Cl_2; (f) NaOH, H_2O, EtOH, then H_3O^+; (g) **6**, **8,** or related amine, DCC, HOBT, DMF; (h) CF_3COOH, CH_2Cl_2; optionally followed by NaOH in H_2O for methyl esters.

appropriate amine component, after which protecting group removal provided the final products **24**. Protection of the amino group proved unnecessary, since the nucleophilicity of the pyridylamine was sufficiently low that it did not interfere with subsequent coupling of **23b.**

Amine **21** could also be used to allow introduction of basic groups after incorporation of the acidic chain, as shown in Scheme 5. Protection as the benzyl carbamate gave **25**, but saponification of this compound was problematic, since the ester was resistant to mild

Scheme 5. Variation of the Basic Group Late in the Synthesis[a]



[a] Reagents: (a) BzOOCCl, Et_3N, CH_2Cl_2; (b) LiOH, H_2O, THF; (c) **8**, DCC, HOBT, DMF; (d) $Pd(OH)_2$, 1,4-cyclohexadiene, MeOH, △; (e) see Experimental Section; (f) CF_3COOH, CH_2Cl_2.

hydrolysis while harsher conditions caused loss of the Cbz group. Lithium hydroxide provided **26** in about 50% yield after several days at room temperature. Coupling with **8** (R = tBu, Ar = mesityl) followed by hydrogenolysis of the Cbz group gave **28**, which could be allowed to react with an electrophilic amidine derivative to give, after deprotection, **29**.

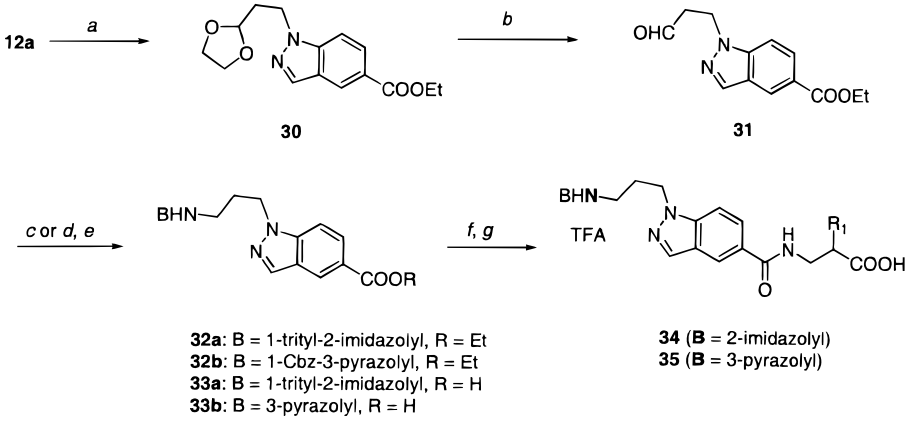
Other basic groups were more easily introduced by reductive amination of the aldehyde **31** with the appropriate heterocyclic amine, as shown in Scheme 6. Unfortunately, in contrast to the success achieved with acrylonitrile, acrolein could not be induced to undergo conjugate addition with **12a**. Therefore, alkylation with the protected bromoaldehyde followed by removal of the undesired 2-alkylated product by chromatography provided **30** in 55% yield. Acidic deprotection afforded **31** quantitatively. Reductive amination with 1-trityl-2-aminoimidazole[22] or 1-Cbz-3-aminopyrazole[37] gave **32a** or **32b**, respectively. The usual sequence of saponification, coupling, and deprotection provided the desired products. In the case of the trityl-protected aminoimidazole derivatives, trityl removal could be achieved by heating in trifluoroacetic acid. *tert*-Butyl esters were removed in the same step, or methyl esters could be subsequently cleaved with lithium hydroxide. Alternatively, the trityl group could be removed without affecting the *tert*-butyl ester by heating in methanol/acetic acid, followed by removal of the ester with TFA at room temperature.

The imidazole amide **39** was synthesized according to Scheme 7. In contrast to acrolein, methyl acrylate underwent conjugate addition with **12a** to provide the bis-ester **36** in quantitative yield. The side chain methyl ester was selectively saponified with lithium hydroxide, and **37** was coupled with 2-aminoimidazole giving **38**. Saponification of the remaining ester with sodium hydroxide, followed by coupling and deprotection, provided **39**.

Variation of the α-substituent (corresponding to the so-called exosite-binding group in GPIIbIIIa antagonists[38]) was achieved by coupling with the appropriate diaminopropionate derivative **8** or other amine as illustrated above or more efficiently late in the synthesis as shown in Scheme 8. (The latter approach has also been used for α-substituent variation in isoxazoline GPIIb/IIIa antagonists.[39,40]) The appropriate α-Cbz derivative **40** (B = 2-pyridyl or 1-trityl-2-imidazolyl) was deprotected by hydrogenolysis, and the resulting amine **41** was functionalized using an acid or acid chloride, chloroformate ester, sulfonyl chloride, sulfamoyl chloride,[40] or isocyanate to give the corresponding amide, carbamate, sulfonamide, sulfamide, or urea, respectively. Removal of the ester completed the synthesis; in the imidazole case the trityl and *tert*-butyl esters were removed in one step with boiling trifluoroacetic acid.

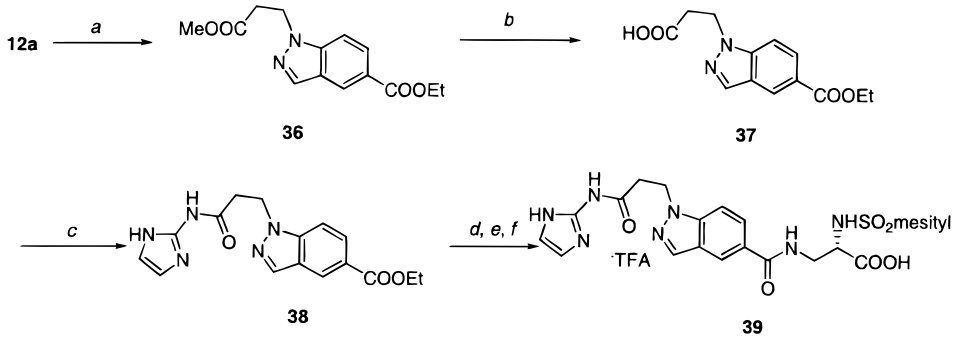
The reversed amide **49** was prepared from 5-nitroindazole **43** (Scheme 9), which was elaborated to **44** using the same procedures as outlined earlier (Scheme 6) for the preparation of **31**. The aminopyridine group was introduced by reductive amination of **44**. The nitro

Scheme 6. Basic Group Introduction by Reductive Amination[a]



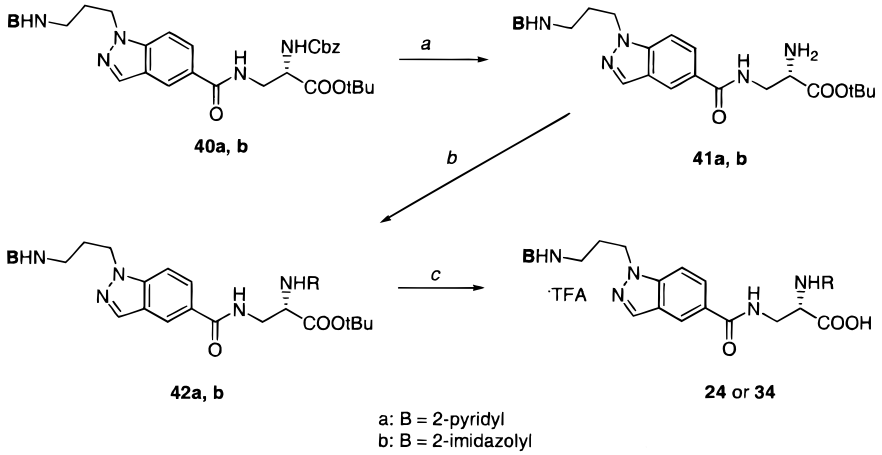
[a] Reagents: (a) $NaN(TMS)_2$, 2-(2-bromoethyl)-1,3-dioxolane, THF, △; (b) HOAc, H_2O, △; (c) 1-trityl-2-aminoimidazole, toluene, △ ($-H_2O$), $NaBH(OAc)_3$ (d) 1-Cbz-3-aminopyrazole, $NaBH(OAc)_3$, $ClCH_2CH_2Cl$; (e) NaOH, H_2O, EtOH, △; (f) **6**, **8,** or related amine, DCC, HOBT, DMF; (g) see text.

Scheme 7. Imidazole Amide Preparation[a]



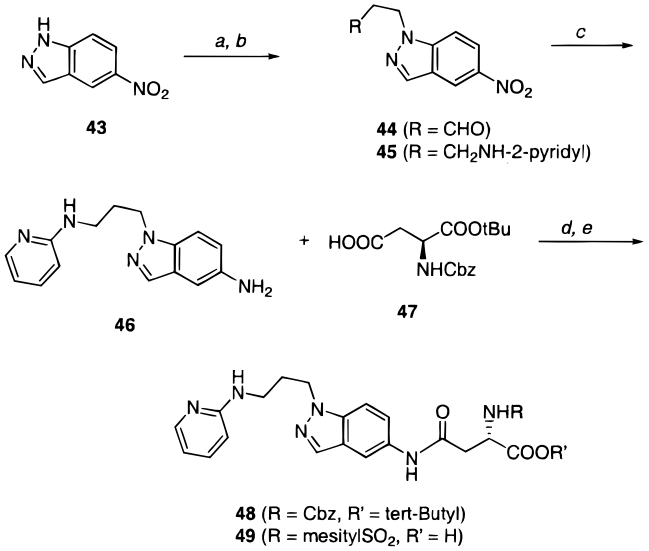
[a] Reagents: (a) methyl acrylate, tBuOH, KOtBu, THF, △; (b) LiOH, H_2O, THF; (c) 2-aminoimidazole sulfate, iPr_2NEt, BOP, DMF, 70 °C; (d) LiOH, H_2O, THF; (e) **8** (R = tBu, Ar = mesityl), DCC, HOBT, DMF; (f) CF_3COOH, CH_2Cl_2.

Scheme 8. Variation of α-Substituent Late in the Synthesis[a]



[a] Reagents: (a) H_2, Pd/C, EtOH; (b) see Experimental Section; (c) CF_3COOH, CH_2Cl_2.

Scheme 9. Preparation of Retro-Amide **49**[a]



[a] Reagents: (a) see Scheme 5; (b) Fe, HOAc, 90 °C; (c) DCC, HOBT, DMF; (d) see Scheme 7.

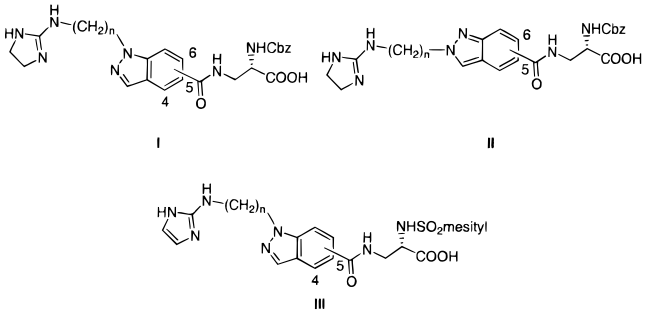
group of **45** was reduced in 80% yield, and coupling of **46** with commercially available **47** followed by deprotection provided **48**, which was converted to **49** as described in Scheme 8.

Results and Discussion

Early structure−activity studies were guided by a purified $\alpha_v\beta_3$ receptor binding assay ($\alpha_v\beta_3$ ELISA).[41] Once IC_{50} values fell much below 1 nM, however, this assay was not useful for distinguishing among different compounds. A functional $\alpha_v\beta_3$ antagonism assay was used instead, involving adhesion of β_3-transfected 293 cells to fibrinogen ($\alpha_v\beta_3$ 293β_3).[22,42] For assessment of selectivity with respect to GPIIbIIIa antagonism, inhibition of aggregation of human gel-purified platelets (GPIIbIIIa GPP) was used. GPP was preferred over the more commonly used platelet-rich plasma aggregation assay since in the latter system differences in plasma protein binding among different compounds would complicate SAR analysis. ELISA and GPP results are based on single determinations; historically these assays have shown standard errors of about 25% or less. The 293β_3 results were averaged from three determinations; the innately higher variability of such a cell-based adhesion assay is reflected in the standard errors of some of these values. For comparison, results for compound **4b**[22] are given in Tables 2 and 3.

Initially, the effects of changes in gross structural features of **18a** were studied by varying the length of the chain bearing the basic moiety and by varying the relative positions of the acidic and basic chains about the indazole core (Table 1). In these early studies, 2-aminoimidazoline served as the basic group, since this was found previously to provide better potency for $\alpha_v\beta_3$ and selectivity over GPIIbIIIa than guanidine itself.[20,22] The 1,5-isomer was much more potent than the 1,6-isomer and similar to the 1,4-isomer (compare $\alpha_v\beta_3$ ELISA IC_{50} values for **18a**, **18b,** and **18c**). The 1,4- and

Table 1. Effect of Substituent Orientation and Basic Chain Length



I II

III

Compd	Structure	Isomer	n	$\alpha_v\beta_3$ ELISA IC_{50}, nM [a]	$\alpha_v\beta_3$ 293β_3 IC_{50} ± SEM, nM [b]
18a	**I**	1,5	3	3.8	460±90
19a	**II**	2,5	3	55	>1000
18b	**I**	1,6	3	1500	>1000
19b	**II**	2,6	3	25	>1000
18c	**I**	1,4	3	7.3	>1000
18d	**I**	1,5	2	51	>1000
18e	**I**	1,5	4	250	>1000
34a	**III**	1,5	3	<0.1	2.3±1.2
34b	**III**	1,4	3	<0.1	25±16

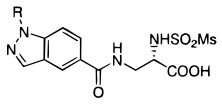
[a] 1 determination. [b] Average of 3 determinations.

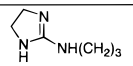
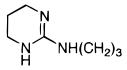
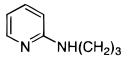
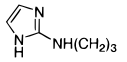
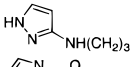
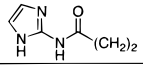
1,5-isomers were also compared in a series having an α-substituent and basic moiety which provided better potency (see below); in this case (**34b** vs **34a**) the $\alpha_v\beta_3$ ELISA values were similar but the preference for the 1,5-isomer in the 293β_3 assay was clear. The analogues with the basic chain at the 2-position (**19a** and **19b**), obtained as minor isomers during attachment of this chain by alkylation, were active but significantly less potent than the 1,5-isomer. Changing the length of the basic chain to either two (**18d**) or four (**18e**) methylenes greatly reduced activity.

Variation of the guanidine replacement was evaluated in the 1,5-disubstituted series, with α-mesitylenesulfonylamino as the α-substituent (Table 2). Expanding the imidazoline ring of **29a** to tetrahydropyrimidine **29b** increased potency against $\alpha_v\beta_3$ without changing GPIIbIIIa potency, leading to some selectivity. Selectivity was increased by replacement with 2-aminopyridine or 2-aminoimidazole. The aminopyridine **24a** maintained similar potency against $\alpha_v\beta_3$ as **29a** but reduced GPIIbIIIa activity. Aminoimidazole **34a**, on the other hand, dramatically increased $\alpha_v\beta_3$ potency.

The 2-aminoimidazole amide **39** was similar to the 2-aminopyridine **24a** but was much less potent than **34a**, in contrast to the findings in the isoxazoline series represented by **4b**.[22] Like **4b**, the basic moiety of **39** offered greater selectivity with respect to GPIIbIIIa (70-fold) than most other indazole derivatives examined. 3-Aminopyrazole **35** was essentially inactive, presumably due to the severely reduced basicity and also because the tautomer shown in Table 2, with no NH available on the ring nitrogen corresponding to that in **34a** or protonated **24**, is the preferred one.[43] In summary, 2-aminopyridine and 2-aminoimidazole provide

Table 2. Effect of Basic Group



Compd	R	$\alpha_v\beta_3$ 293β_3 IC_{50} ± SEM, nM [a]	GPIIbIIIa GPP IC_{50}, nM [b]	GPP / 293β3
29a		70±21	57	0.8
29b		28±24	66	2.4
24a		48±14	220	4.6
34a		2.3±1.2	21	9.1
35		>1000	nd	
39		56±26	4000	71
4b		31±16	61000	2000

[a] Average of 3 determinations. [b] 1 determination; nd = not determined.

good enhancement of the potency of the indazole series relative to 2-aminoimidazoline, and both of these basic groups were used in further SAR exploration.

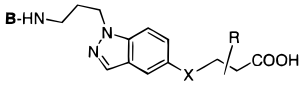
The nature of the acidic chain also had a profound influence on potency against $\alpha_v\beta_3$ as shown in Table 3. In the aminopyridine series, reversing the amide from **24a** to **49** caused a 10−20-fold loss in potency, and N-methylation of the normal amide (**24b**) was even worse. This suggests that the NH of the amide is important for interaction with the receptor.

In agreement with findings in the isoxazoline series represented by **4a** and **4b,**[21,22] the substituent α to the carboxylate was also necessary for activity, as shown by the inactivity of **24c** and **34f**. In GPIIbIIIa antagonists, lipophilic substituents α to the carboxylate were found to enhance potency and duration of action through presumed binding to a lipophilic pocket on the receptor, labeled the "exosite".[38] Whereas this substituent was not absolutely necessary for good GPIIbIIIa binding,[39] it appears critical for binding of this series of compounds to $\alpha_v\beta_3$. The presence of an exosite-binding group is not sufficient for activity, though, since the aminoimidazole compound **34e**, which bears one of the better α-substituents (see below) but lacks the carboxylate moiety, is inactive. The stereochemistry of the α-substituted carboxylate is important, since the (*R*)-isomer **34d** is 100-fold less potent than the (*S*)-isomer **34a**.

Moving the exosite-binding group β to the carboxylate, providing aspartate derivatives such as **24e** and **24f**, also led to inactive compounds. This also contrasts to GPIIbIIIa antagonists such as the series represented by **3**, where aspartate amide or other β-substituted β-alanine moieties could replace diaminopropionate derivatives and still give useful binding to the receptor, although with somewhat reduced potency.[39]

The nature of the functionality attaching the exosite-binding group was important for potency against $\alpha_v\beta_3$ (Table 3). While carbamates such as **24d** and **24g** were active at 200−300 nM, isosteric amides (**24j**, **24k**) and ureas (**24i**) were at least 3-fold less active. This might reflect a difference in conformational preference for the

Table 3. Effect of Acidic Substituent



Compd	B[a]	X	R	$\alpha_v\beta_3$ 293β_3 IC_{50} ± SEM, nM[b]	GPIIbIIIa GPP IC_{50}, nM[c]	GPP / 293β3
24a	2-pyr	-CONH-	α-(S)-NHSO$_2$mesityl	48±14	220	4.5
49	2-pyr	-NHCO-	α-(S)-NHSO$_2$mesityl	840±410	41000	48
24b	2-pyr	-CON(Me)-	α-(S)-NHSO$_2$mesityl	>1000	nd	
24c	2-pyr	-CONH-	H	>1000	nd	
24d	2-pyr	-CONH-	α-(S)-NHCO$_2$CH$_2$Ph	300±140	>10000	>33
24e	2-pyr	-CONH-	β-(S)-CONH(CH$_2$)$_2$Ph	>1000	nd	
24f	2-pyr	-CONH-	β-(S)-CONHmesityl	>1000	nd	
24g	2-pyr	-CONH-	α-(S)-NHCOOiBu	240±65	25000	100
24h	2-pyr	-CONH-	α-(S)-NHCONHPh	>1000	nd	
24i	2-pyr	-CONH-	α-(S)-NHCONHCH$_2$Ph	>1000	nd	
24j	2-pyr	-CONH-	α-(S)-NHCO(CH$_2$)$_2$Ph	>1000	nd	
24k	2-pyr	-CONH-	α-(S)-NHCOCH$_2$iBu	>1000	nd	
24m	2-pyr	-CONH-	α-(S)-NHSO$_2$Ph	120±85	290	2.4
24n	2-pyr	-CONH-	α-(S)-NHSO$_2$nBu	360±60	9000	25
24p	2-pyr	-CONH-	α-(S)-NHSO$_2$CH$_2$Ph	>1000	nd	
24q	2-pyr	-CONH-	α-(S)-NHSO$_2$NHiBu	>1000	nd	
24r	2-pyr	-CONH-	α-(S)-NHSO$_2$NHCH$_2$Ph	600±350	8100	14
24s	2-pyr	-CONH-	α-(S)-NHSO$_2$NHPh	170±83	7800	46
24t	2-pyr	-CONH-	α-(S)-NHSO$_2$NHmesityl	360±100	36000	100
34c	2-im	-CONH-	α-(S)-NHCO$_2$CH$_2$Ph	74±47	1000	14
34a	2-im	-CONH-	α-(S)-NHSO$_2$mesityl	2.3±1.2	21	9.1
34d	2-im	-CONH-	α-(R)-NHSO$_2$mesityl	290±120	5000	17
34e	2-im	-CONH-	NHSO$_2$mesityl[d]	>1000	nd	
34f	2-im	-CONH-	H	>1000	nd	
4b				31±16	61000	2000

[a] 2-pyr = pyrid-2-yl; 2-im = imidazol-2-yl. [b] Average of 3 determinations. [c] 1 determination; nd = not determined. [d] Descarboxy.

carbamates or might suggest that the ether-type oxygen of the carbamate is important for binding to the receptor. This finding also contrasts with the SAR observed for isoxazoline GPIIbIIIa antagonists, where similar potency was observed for these three types of exosite-binding groups.[39]

However, in accordance with findings from GPIIbIIIa research,[40] aryl sulfonamides (**24m**, **24a**) and sulfamides (**24s**, **24t**) provided the same or better potency when compared to the carbamates. Alkyl (**24n**, **24q**) or benzyl (**24p**, **24r**) sulfonamide and sulfamide analogues were less potent. One possibility for the qualitative similarity between sulfonamide and carbamate α-substituents was suggested by examination of molecular models of *N*-methyl benzyl carbamate and *N*-methyl benzenesulfonamide (Figure 1: structures were minimized with MM2, NH protons are shown in purple). Superimposing the nitrogens and the methyl carbons (used as mimics for the points of attachment of the nitrogens in **24d** and **24m**) allows both pairs of oxygen atoms to overlap quite well. Since only these two functional groups, along with the similar sulfamide, conferred good activity, perhaps these two oxygens are more important for $\alpha_v\beta_3$ receptor interaction than is the case for GPIIbIIIa. The differences in potency between carbamate and sulfonamide may reflect the differences in positioning of the aromatic rings relative to the functional groups, seen in Figure 1.

Since many sulfonyl chlorides are commercially available or easily prepared, the sulfonamide moiety was

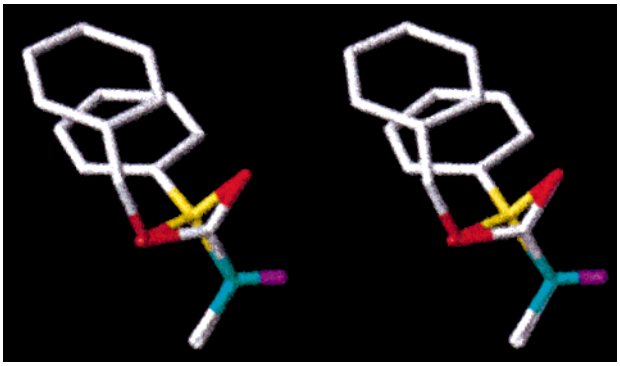
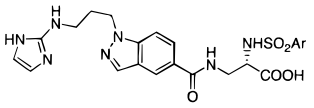


Figure 1. Stereoview of the overlap between *N*-methyl benzyl carbamate and *N*-methyl benzenesulfonamide.

Table 4. Effect of Sulfonamide Aromatic Group



Compd	Ar	$\alpha_v\beta_3$ 293β_3 IC_{50} ± SEM, nM[a]	GPIIbIIIa GPP IC_{50}, nM[b]	GPP / 293β3
34g	Ph	44±12	34	0.8
34h	4-Me-Ph	16±0.1	83	5.2
34i	4-Cl-Ph	10±0.1	260	26
34j	4-MeO-Ph	26±9.8	410	16
34k	4-CF_3-Ph	52±16	4400	85
34m	4-AcNH-Ph	150±25	400	2.7
34n	4-t-butyl-Ph	120±51	2000	17
34p	4-Ph-Ph	35±15	130	3.7
34q	3,4-Cl_2-Ph	10±6.0	790	79
34r	2,6-Cl_2-Ph	8.5±5.0	12	1.4
34s	2,6-Me_2-Ph	10±2.3	74	7.4
34a	2,4,6-Me_3-Ph	2.3±1.2	21	9.1
34t	2,6-Me_2-4-Ph-Ph	4.9±3.2	74	15
34u	1-naphthyl	13±7.2	39	3
34v	2-naphthyl	4.7±0.95	81	17

[a] Average of 3 determinations. [b] 1 determination.

chosen for exploring the SAR of the aryl ring. The results for the aminoimidazole series are shown in Table 4; very similar comparisons were found in the aminopyridine series, although the $\alpha_v\beta_3$ potencies were generally reduced. All aryl sulfonamides evaluated gave 293β_3 IC_{50} values below 200 nM, while potencies against GPIIbIIIa ranged a bit more widely.

Relative to phenyl (**34g**), 4-substitution with small groups increased potency (**34h**, **34i**, **34j**), while larger and more polar groups (**34m**, **34n**) tended to reduce activity. *p*-Biphenyl (**34p**) was an exception, showing greater potency than would be expected for the size of the substituent. 4-Substitution also generally enhanced selectivity with respect to GPIIbIIIa, with lipophilic substituents (**34k** and **34n**) being more effective. 4-Chloro (**34i**) and 3,4-dichloro (**34q)** substituents provided the best balance of potency and selectivity. Electronic effects of ring substituents on potency were minimal (compare **34h** and **34i**, **34r** and **34s**). Additional meta substitution hardly affected potency (**34i** vs **34q**), and ortho disubstitution (**34r**, **34s**) was similar to para monosubstitution but with differing effects on selectivity over GPIIbIIIa. Para substitution and ortho disubstitution were additive, with very potent compounds resulting (**34a**, **34t**). Adding the para substituent increased the selectivity relative to the ortho disubstituted cases (**34a** or **34t** vs **34s**). Naphthyl derivatives were also potent, with 2-naphthyl **34v** more potent and selective than 1-naphthyl **34u**.

In summary, the indazole ring system provided a useful scaffold for attaching basic and acidic moieties to obtain potent, somewhat selective antagonists of the integrin $\alpha_v\beta_3$. General features of the SARs are similar to those observed for isoxazoline-based antagonists represented by **4b**, with generally greater potency but less selectivity with respect to GPIIbIIIa.[22] The 1,5-disubstituted indazole core with a three-carbon tether attaching the basic moiety was optimal. Groups less basic than guanidine (2-aminopyridine and especially 2-aminoimidazole) enhanced potency along with showing better selectivity over the related integrin GPIIbIIIa. The amide bond in the acidic chain was important for activity, as was the carboxylate group and an α-(*S*)-substituent. Aryl sulfonamides gave the best potency as exosite-binding groups, with the mesitylenesulfonamide analogue **34a** providing excellent potency and 9-fold selectivity with respect to GPIIbIIIa. This compound (SM256) was selected for further investigation, the results of which are published elsewhere.[42,44]

Experimental Section

Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Reactions were run at room temperature under an atmosphere of N_2 unless otherwise indicated. Organic phases from aqueous extractions were dried over $MgSO_4$ or Na_2SO_4, filtered, and concentrated under reduced pressure. Flash chromatography was performed on silica gel using the method of Still.[45] Analytical HPLC was done with a 4.6-mm × 250-mm Dynamax C_{18} column operated at room temperature, eluting at 1.0 mL/min using a 20-min linear gradient from 97.5:2.5 to 20:80 water:acetonitrile, containing 0.05% TFA, with UV detection at 254 nm. Preparative HPLC separations used the same conditions, but with a 41.4-mm × 250-mm column eluted at 40 mL/min over 35 min. ^{1}H NMR data were obtained at 300 MHz using a Varian VXR400 spectrometer and were referenced to TMS. Mass spectral data were obtained on either VG 70-VSE (FAB, high-res FAB, high-res DCI) or Finnigan MAT 8230 (DCI) mass spectrometers. Combustion analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ. Solvents and reagents were used as purchased from commercial sources unless otherwise noted. Quoted yields are of isolated material.

Ethyl Indazole-5-carboxylate (12a). Ethyl 3-methyl-4-aminobenzoate[46] (251 g, 1.4 mol), KOAc (143 g, 1.46 mol), Ac_2O (286 g, 2.8 mol), and $CHCl_3$ (2700 mL) were combined and stirred. The temperature rose to 40 °C, then started to decline, at which time no starting material was detected by TLC. 18-Crown-6 (75 g, 280 mmol) and *n*-amyl nitrite (365 g, 3.1 mol) were added and the mixture was heated at reflux overnight. The cooled mixture was washed with aqueous $NaHCO_3$ and water, dried, and concentrated. The residue was combined with that from another batch (711 g total) and distilled through a 10-cm Vigreaux column to provide **11a** (576 g, 82%): bp 115−165 °C (1.0 Torr). This was stirred overnight with HCl (6 N; 2000 mL) and EtOH (2000 mL). The mixture was concentrated, and the solid was stirred in H_2O. The pH was adjusted to 8 with aqueous NH_3, and the mixture was extracted with

CH_2Cl_2. The organic phase was dried and concentrated to provide a solid, which was recrystallized from MeCN to give **12a** (281 g, 60%) as a tan solid: mp 122−124 °C; ^{1}H NMR ($CDCl_3$) δ 10.23 (bs, 1H), 8.56 (s, 1H), 8.20 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 4.42 (q, J = 7.3 Hz, 2H), 1.42 (t, J = 7.3 Hz, 3H); HRMS (NH_3-CI) m/z 191.0838 [$(M + H)^+$ calcd for $C_{10}H_{11}N_2O_2$ 191.0821]. Anal. ($C_{10}H_{10}N_2O_2$) C, H, N.

Methyl Indazole-6-carboxylate (12b). A solution of methyl 4-methyl-3-aminobenzoate (12.39 g, 75 mmol) and NH_4BF_4 (10.48 g, 100 mmol) in water (85 mL) and concentrated HCl (15 mL) was cooled to 3 °C and treated dropwise over 25 min with a solution of $NaNO_2$ (5.18 g, 75 mmol) in water (12 mL). The resulting thick slurry was stirred for 35 min, and the solid was collected by filtration, rinsed with water, methanol, and ether, and dried under N_2. The solid was added in one portion to a stirred mixure of KOAc (8.1 g, 82.5 mmol) and 18-crown-6 (0.5 g, 1.9 mmol) in $CHCl_3$ (170 mL). After 70 min, water (170 mL) was added, and the layers were separated. The aqueous phase was extracted with $CHCl_3$. The combined organic phases were washed with water, dried, and concentrated. The residue was triturated with hexane and the resulting solid isolated by filtration to provide **12b** (8.85 g, 67%) as a dull yellow powder: mp 142−144 °C (MeCN); ^{1}H NMR ($CDCl_3$) δ 11.17 (bs, 1H), 8.30 (q, J = 1.1 Hz, 1H), 8.18 (d, J = 1.1 Hz, 1H), 7.85 (dd, J = 8.4, 1.1 Hz, 1H), 7.81 (dd, J = 8.4, 1.1 Hz, 1H), 3.97 (s, 3H); MS (NH_3-CI) m/z 177 [$(M + H)^+$, 100%]. Anal. ($C_9H_8N_2O_2$) C, H, N.

Methyl indazole-4-carboxylate (12c) was prepared from methyl 2-methyl-3-aminobenzoate using the procedure for the synthesis of **12b**, as an orange solid: ^{1}H NMR ($CDCl_3$) δ 8.61 (s, 1H), 7.98 (d, J = 7.3 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.42 (dd, J = 8.4, 7.3 Hz, 1H), 4.01 (s, 3H); HRMS (NH_3-CI) m/z 177.0669 [$(M + H)^+$ calcd for $C_9H_9N_2O_2$ 177.0664].

Ethyl 1-(3-[1-Phthalimido]propyl)indazole-5-carboxylate (13a; R = Et, *n* = 3) and Ethyl 2-(3-[1-Phthalimido]-propyl)indazole-5-carboxylate (14a; R = Et, *n* = 3). A solution of potassium bis(trimethylsilyl)amide (0.5 M in toluene; 46.6 mL, 23.3 mmol) and 18-crown-6 (100 mg) in THF (50 mL) was treated with a solution of **12a** (4.43 g, 23.3 mmol) in THF (50 mL), then with a solution of *N*-(3-bromopropyl)-phthalimide (6.24 g, 23.3 mmol) in THF (50 mL). The mixture was heated at reflux for 16 h, then cooled and poured into water (200 mL). The aqueous layer was extracted with EtOAc, and the combined organic layers were dried and concentrated. The residue was purified by flash chromatography (hexanes: EtOAc 50:50) to provide **13a** (R = Et, n = 3) (4.25 g, 48%) as a yellow solid: mp 122−124 °C; ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 8.06 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.82 (m, 2H), 7.71 (m, 2H), 7.42 (d, J = 8.5 Hz, 1H), 4.44 (t, J = 7.5 Hz, 2H), 4.40 (q, J = 7.2 Hz, 2H), 3.80 (t, J = 7.5 Hz, 2H), 2.40 (m, 2H), 1.42 (t, J = 7.2 Hz, 3H); HRMS (NH_3-CI) m/z 378.1430 [$(M + H)^+$ calcd for $C_{21}H_{20}N_3O_4$ 378.1454]. Anal. ($C_{21}H_{19}N_3O_4 \cdot 0.25H_2O$) C, H, N. Also obtained (as a more polar material) was **14a** (R = Et, n = 3) (2.75 g, 31%) as a yellow solid: mp 133−135 °C; ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H), 8.25 (s, 1H), 7.85 (d, J = 8.4 Hz, 1H), 7.81 (m, 2H), 7.70 (m, 2H), 7.61 (d, J = 8.4 Hz, 1H), 4.50 (t, J = 7.5 Hz, 2H), 4.40 (q, J = 7.2 Hz, 2H), 3.78 (t, J = 7.5 Hz, 2H), 2.47 (m, 2H), 1.43 (t, J = 7.2 Hz, 3H); HRMS (NH_3-CI) m/z 378.1430 [$(M + H)^+$ calcd for $C_{21}H_{20}N_3O_4$ 378.1454]. Anal. ($C_{21}H_{19}N_3O_4 \cdot 0.1H_2O$) C, H, N.

Ethyl 1-(3-[*N*-4,5-Dihydroimidazol-2-ylamino]propyl)-indazole-5-carboxylate (16a; R = Et, *n* = 3). A mixture of **13a** (R = Et, n = 3; 4.20 g, 11.1 mmol), EtOH (75 mL), THF (75 mL), and anhydrous H_2NNH_2 (1.5 mL) was stirred for 16 h. THF (100 mL) was added, the mixture was filtered, and the filtrate was concentrated to provide **15a** (R = Et, n = 3) as an orange syrup, which was used without purification: ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.10 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 4.52 (t, J = 7.5 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 2.68 (t, J = 7.5 Hz, 2H), 2.06 (m, 2H), 1.47 (bs, 2H), 1.43 (t, J = 7.2 Hz, 3H); HRMS (NH_3-CI) m/z 248.2392 [$(M + H)^+$ calcd for $C_{13}H_{18}N_3O_2$ 248.1399]. A mixture of this material, 2-methylthio-4,5-dihydroimidazole hydriodide (2.71 g, 11.1 mmol), and pyridine (125 mL) was heated at 80 °C for 5 h. The mixture was cooled and concentrated, and the residue was purified by flash chromatography (CH_2Cl_2:MeOH 80:20) to provide **16a** (R = Et, n = 3) (3.73 g, 75%) as a gum: ^{1}H NMR (DMSO-d_6) δ 8.50 (s, 1H), 8.30 (s, 1H), 8.24 (bs, 1H), 7.98 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.3 Hz, 1H), 4.49 (t, J = 7.6 Hz, 2H), 4.34 (q, J = 7.3 Hz, 2H), 3.57 (s, 4H), 3.13 (m, 2H), 2.05 (m, 2H), 1.35 (t, J = 7.3 Hz, 3H); HRMS (NH_3-CI) m/z 316.1765 [$(M + H)^+$ calcd for $C_{16}H_{22}N_5O_2$ 316.1774].

3-[1-[3-(*N*-4,5-Dihydroimidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)-propionic Acid Trifluoroacetate (18a). A mixture of **16a** (R = Et, n = 3; 3.39 g, 7.64 mmol), aqueous NaOH (1.0 M; 16 mL, 16 mmol), and EtOH (35 mL) was stirred at reflux for 16 h, then cooled and treated with aqueous HCl (1.0 M; 16 mL, 16 mmol). The solvent was removed under vacuum, benzene was added, and solvent was again removed. A portion of the resulting residue (77 mg, 240 μmol) was combined with **6**[25] (70 mg, 240 μmol), DCC (60 mg, 313 μmol), HOBT (10 mg), DMF (5 mL), and Et_3N (0.1 mL), and the resulting mixture was stirred for 16 h. The mixture was concentrated and the residue was purified by flash chromatography (CH_2Cl_2:MeOH 90:10) to provide **17a** (n = 3; 122 mg, 85%) as a yellow gum: ^{1}H NMR (DMSO-d_6) δ 8.53 (bm, 1H), 8.30 (s, 1H), 8.24 (s+m, 2H), 7.88 (d, J = 8.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.70 (m, 1H), 7.34 (m, 5H), 5.04 (s, 2H), 4.47 (t, J = 7.4 Hz, 2H), 4.23 (m, 1H), 3.75−3.50 (m, 2H), 3.55 (s, 4H), 3.12 (q, J = 7.4 Hz, 2H), 2.06 (m, 2H), 1.33 (s, 9H); HRMS (NH_3-CI) m/z 564.2959 [$(M + H)^+$ calcd for $C_{29}H_{38}N_7O_5$ 564.2934]. A solution of this material (108 mg, 180 μmol) in CH_2Cl_2 (5 mL) and TFA (0.5 mL) was stirred overnight and concentrated. The residue was triturated in ether to provide **18a** (74 mg, 75%) as a hygroscopic, off-white amorphous solid: ^{1}H NMR (DMSO-d_6) δ 8.57 (bt, 1H), 8.31 (s, 1H), 8.28 (m, 1H), 8.24 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.62 (m, 1H), 7.32 (m, 5H), 5.02 (s, 2H), 4.47 (t, J = 7.6 Hz, 2H), 4.29 (m, 1H), 3.65 (m, 2H), 3.55 (s, 4H), 3.11 (m, 2H), 2.06 (m, 2H); HRMS (FAB) m/z 508.2323 [$(M + H)^+$ calcd for $C_{25}H_{30}N_7O_5$ 508.2308]. Anal. ($C_{25}H_{29}N_7O_5 \cdot 1.4CF_3COOH \cdot 1.2H_2O$) C, H, N, F.

Using the procedures described for preparing **18a** via **13a** and **16a**, the following compounds were prepared.

3-[1-[3-(*N*-4,5-Dihydroimidazol-2-ylamino)propyl]indazol-6-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)-propionic acid trifluoroacetate (18b): from **12b**, as an off-white amorphous solid; ^{1}H NMR (MeOH-d_4) δ 8.12 (s, 1H), 8.01 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.3−7.1 (5H), 5.06 (ab, J = 12.5 Hz, 2H), 4.6−4.5 (m, 3H), 3.88 (dd, J = 13.7, 4.6 Hz, 1H), 3.72 (dd, J = 13.7, 8.3 Hz, 1H), 3.57 (s, 4H), 3.10 (t, J = 6.6 Hz, 2H), 2.18 (m, 2H); HRMS (FAB) m/z 508.2324 [$(M + H)^+$ calcd for $C_{25}H_{30}N_7O_5$ 508.2308]. Anal. ($C_{25}H_{29}N_7O_5 \cdot CF_3COOH$) C, H, N, F.

3-[1-[3-(*N*-4,5-Dihydroimidazol-2-ylamino)propyl]indazol-4-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)-propionic acid trifluoroacetate (18c): from **12c**, as a hygroscopic, off-white amorphous solid; ^{1}H NMR (MeOH-d_4) δ 8.38 (s, 1H), 7.75 (d, J = 8.1 Hz, 1H), 7.50 (m, 2H), 7.3−7.2 (m, 5H), 5.06 (ab, J = 12.5 Hz, 2H), 4.46 (m, 1H), 4.53 (t, J = 6.6 Hz, 2H), 3.90 (m, 1H), 3.73 (m, 1H), 3.60 (s, 4H), 3.14 (t, J = 6.6 Hz, 2H), 2.17 (m, 2H); HRMS (FAB) m/z 508.2313 [$(M + H)^+$ calcd for $C_{25}H_{30}N_7O_5$ 508.2308]. Anal. ($C_{25}H_{29}N_7O_5 \cdot 1.4CF_3COOH$) C, H, N, F.

3-[1-[2-(*N*-4,5-Dihydroimidazol-2-ylamino)ethyl]indazol-5-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)-propionic acid trifluoroacetate (18d): from **12a** and *N*-(2-bromoethyl)phthalimide, as a white amorphous solid; ^{1}H NMR (MeOH-d_4) δ 8.25 (s, 1H), 8.18 (s, 1H), 7.88 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.3−7.2 (5H), 5.06 (ab, J = 12.5 Hz, 2H), 4.59 (t, J = 5.5 Hz, 2H), 4.50 (dd, J = 8.3, 4.6 Hz, 1H), 3.87 (dd, J = 13.8, 4.6 Hz, 1H), 3.70 (m, 3H), 3.47 (s, 4H); MS (ESI) m/z 494.3 (100%, $M + H)^+$; HRMS (FAB) m/z 494.2133 [$(M + H)^+$ calcd for $C_{24}H_{28}N_7O_5$ 494.2152]. Anal. ($C_{24}H_{27}N_7O_5 \cdot 1.15CF_3COOH \cdot H_2O$) C, H, N, F.

3-[1-[4-(*N*-4,5-Dihydroimidazol-2-ylamino)butyl]indazol-5-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)-propionic acid trifluoroacetate (18e): from **12a** and *N*-(4-bromobutyl)phthalimide, as a white amorphous solid; ^{1}H NMR (MeOH-d_4) δ 8.24 (s, 1H), 8.12 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.62 (d, J = 8.8 Hz, 1H), 7.3−7.2 (5H), 5.06 (ab, J = 12.8 Hz, 2H), 4.5 (m, 3H), 3.86 (dd, J = 13.7, 4.6 Hz, 1H), 3.71 (dd, J = 13.7, 8.4 Hz, 1H), 3.62 (s, 4H), 3.15 (t, J = 6.6 Hz, 2H), 1.95 (m, 2H), 1.52 (m, 2H); HRMS (FAB) m/z 522.2479 [(M + H)$^+$ calcd for $C_{26}H_{32}N_7O_5$ 522.2465]. Anal. ($C_{26}H_{31}N_7O_5$·1.15CF_3-$COOH$·H_2O) C, H, N, F.

3-[2-[3-(*N*-4,5-Dihydroimidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)-propionic acid trifluoroacetate (19a): from **14a** (R = Et, n = 3), as a white amorphous solid; ^{1}H NMR (MeOH-d_4) δ 8.39 (s, 1H), 8.24 (s, 1H), 7.69 (d, J = 8.8 Hz, 1H), 7.63 (d, J = 8.8 Hz, 1H), 7.3−7.2 (5H), 5.06 (ab, J = 12.5 Hz, 2H), 4.55 (t, J = 6.6 Hz, 2H), 4.50 (dd, J = 8.4, 4.8 Hz, 1H), 3.85 (dd, J = 13.8, 4.8 Hz, 1H), 3.71 (dd, J = 13.8, 8.4 Hz, 1H), 3.67 (s, 4H), 3.22 (t, J = 6.6 Hz, 2H), 2.25 (m, 2H); HRMS (FAB) m/z 508.2308 [(M + H)$^+$ calcd for $C_{25}H_{30}N_7O_5$ 508.2308]. Anal. ($C_{25}H_{29}N_7O_5$·1.2CF_3COOH·0.8H_2O) C, H, N, F.

3-[2-[3-(*N*-4,5-Dihydroimidazol-2-ylamino)propyl]indazol-6-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)-propionic acid trifluoroacetate (19b): from **12b** via **14b**, as a white amorphous solid; ^{1}H NMR (MeOH-d_4) δ 8.30 (s, 1H), 8.11 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.3−7.1 (m, 5H), 5.06 (ab, J = 12.5 Hz, 1H), 4.56 (t, J = 6.6 Hz, 2H), 4.52 (dd, J = 8.1, 4.8 Hz, 1H), 3.86 (dd, J = 13.9, 4.8 Hz, 1H), 3.72 (dd, J = 13.9, 8.2 Hz, 1H), 3.66 (s, 4H), 3.21 (t, J = 6.6 Hz, 2H), 2.25 (m, 2H); HRMS (FAB) m/z 508.2285 [(M + H)$^+$ calcd for $C_{25}H_{30}N_7O_5$ 508.2308]. Anal. ($C_{25}H_{29}N_7O_5$·1.5CF_3-$COOH$) C, H, N, F.

Ethyl 1-(2-Cyanoethyl)indazole-5-carboxylate (20). A solution of **12a** (76 g, 400 mmol), acrylonitrile (158 mL, 2.4 mol), and sodium bis(trimethylsilyl)amide (1.0 M in THF; 20.0 mL, 20.0 mmol) in EtOH (800 mL) was heated to reflux. After 2 h the solution was cooled and treated with HCl (1.0 M; 30 mL, 30 mmol). Partial concentration under vacuum provided a solid. Water (2000 mL) was added and the solid was collected by filtration, rinsed with water, and dried to provide **20** (87.6 g, 90%) as a pale yellow fluffy solid: mp 106−109 °C; ^{1}H NMR ($CDCl_3$) δ 8.54 (s, 1H), 8.16 (s, 1H), 8.13 (d, J = 9.1 Hz, 1H), 7.48 (d, J = 9.1 Hz, 1H), 4.70 (t, J = 6.6 Hz, 2H), 4.42 (q, J = 7.0 Hz, 2H), 3.03 (t, J = 6.6 Hz, 2H), 1.43 (t, J = 7.0 Hz, 3H); HRMS (NH_3-CI) m/z 244.1070 [(M + H)$^+$ calcd for $C_{13}H_{14}N_3O_2$ 244.1086]. Anal. ($C_{13}H_{13}N_3O_2$) C, H, N.

Ethyl 1-(3-Aminopropyl)indazole-5-carboxylate Hydrochloride (21). A mixture of **20** (60 g, 260 mmol), PtO_2 (6.0 g), EtOH (1600 mL), and $CHCl_3$ (200 mL) was shaken in a pressure bottle under H_2 (40 psig) for 19 h. The mixture was filtered through Celite and the solids were washed with EtOH. The filtrate was concentrated and the residue was dissolved in aqueous $NaHCO_3$ and washed with EtOAc. The aqueous phase was acidified with HCl and concentrated to provide crude **21** in quantitative yield. This was recrystallized (EtOH) to provide a white solid (36.6 g, 57%): mp 198−200 °C; ^{1}H NMR (DMSO-d_6) δ 8.49 (s, 1H), 8.32 (s, 1H), 8.07 (bs, 3H), 7.98 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 4.58 (t, J = 6.8 Hz, 2H), 4.34 (q, J = 7.0 Hz, 2H), 2.80 (bm, 2H), 2.14 (m, 2H), 1.34 (t, J = 7.0 Hz, 3H); HRMS (NH_3-CI) m/z 248.1396 [(M + H)$^+$ calcd for $C_{13}H_{18}N_3O_2$ 248.1399]. Anal. ($C_{13}H_{17}N_3O_2$·1.05HCl) C, H, N, Cl.

Ethyl 1-(3-[*N*-(1-Oxido-2-pyridyl)amino]propyl)indazole-5-carboxylate (22a). A mixture of **21** (600 mg, 2.4 mmol), 2-chloropyridine 1-oxide hydrochloride (806 mg, 4.9 mmol), $NaHCO_3$ (816 mg, 9.7 mmol), and nBuOH (7 mL) was stirred at 100 °C for 21 h, then was cooled and filtered. The filtrate was concentrated and the residue was purified by flash chromatography (CH_2Cl_2:MeOH 95:5) to provide **22a** (675 mg, 81%) as a pale yellow solid: mp 87−89 °C; ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 1H), 8.15 (s, 1H), 8.13 (dd, J = 6.6, 1.1 Hz, 1H), 8.03 (dd, J = 8.8, 1.5 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.10 (t, J = 7.3 Hz, 1H), 6.93 (bm, 1H), 6.56 (t, J = 6.6 Hz, 1H), 6.41 (dd, J = 8.4, 1.5 Hz, 1H), 4.57 (t, J = 6.6 Hz, 2H), 4.40 (q, J = 7.0 Hz, 2H), 3.24 (q, J = 6.6 Hz, 2H), 2.38 (m, 2H), 1.40 (t, J = 7.0 Hz, 3H); HRMS (NH_3-CI) m/z 341.1622 [(M + H)$^+$ calcd for $C_{18}H_{21}N_4O_3$ 341.1614]. Anal. ($C_{18}H_{20}N_4O_3$) C, H, N.

Ethyl 1-(3-[*N*-(2-Pyridyl)amino]propyl)indazole-5-carboxylate (22b). 22a (2.90 g, 8.5 mmol), 10% Pd on charcoal (580 mg), and EtOH (50 mL) were shaken under H_2 (60 psig) for 60 h. The mixture was filtered through Celite and the solids were rinsed with EtOH. Concentration provided **22b** (2.40 g, 88%) as a glass: ^{1}H NMR ($CDCl_3$) δ 8.52 (s, 1H), 8.12 (s, 1H), 8.06 (m, 2H), 7.38 (m, 2H), 6.55 (m, 1H), 6.32 (m, 1H), 4.70 (bm, 1H), 4.53 (t, J = 6.6 Hz, 2H), 4.40 (q, J = 7.3 Hz, 2H), 3.30 (m, 2H), 2.24 (m, 2H), 1.42 (t, J = 7.3 Hz, 3H); HRMS (NH_3-CI) m/z 325.1659 [(M + H)$^+$ calcd for $C_{18}H_{21}N_4O_2$ 325.1665].

1-(3-[*N*-(2-Pyridyl)-*N*-*tert*-butoxycarbonylamino]propyl)indazole-5-carboxylic Acid (23a). A solution of **22b** (2.25 g, 6.9 mmol), CH_2Cl_2 (75 mL), Et_3N (1.5 mL), and *N*,*N*-dimethylaminopyridine (225 mg) was stirred at 0 °C. Di-*tert*-butyl dicarbonate (2.26 g, 10.3 mmol) was added and the mixture was stirred for 16 h. Concentration and purification by flash chromatography (hexanes:EtOAc 65:35) gave the Boc-protected amine (1.92 g, 65%) as a clear oil: ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 1.5 Hz, 1H), 8.28 (m, 1H), 8.08 (s, 1H), 8.04 (dd, J = 8.8, 1.5 Hz, 1H), 7.60 (m, 2H), 7.37 (d, J = 8.8 Hz, 1H), 6.99 (m, 1H), 4.46 (t, J = 7.3 Hz, 2H), 4.41 (q, J = 7.0 Hz, 2H), 4.02 (m, 2H), 2.34 (m, 2H), 1.42 (t, J = 7.0 Hz, 3H), 1.42 (s, 9H); HRMS (NH_3-CI) m/z 425.2193 [(M + H)$^+$ calcd for $C_{23}H_{29}N_4O_4$ 425.2189]. A mixture of this material (1.8 g, 4.2 mmol), water (25 mL), EtOH (25 mL), and aqueous NaOH (1.0 M; 9 mL, 9 mmol) was heated at reflux for 16 h. The mixture was cooled and acidified with HCl (1.0 M; 10 mL, 10 mmol) to give a gum. The liquid was decanted and the residue was triturated several times with hexane to provide **23a** (1.27 g, 75%) as a solid: mp 129−131 °C; ^{1}H NMR ($CDCl_3$) δ 8.59 (s, 1H), 8.30 (m, 1H), 8.12 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.61 (m, 2H), 7.41 (d, J = 8.8 Hz, 1H), 7.00 (m, 1H), 4.46 (t, J = 7.2 Hz, 2H), 4.01 (t, J = 7.2 Hz, 2H), 2.34 (m, 2H), 1.42 (s, 9H); HRMS (NH_3-CI) m/z 397.1878 [(M + H)$^+$ calcd for $C_{21}H_{25}N_4O_4$ 397.1876]. Anal. ($C_{21}H_{24}N_4O_4$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)propionic Acid Trifluoroacetate (24d). A mixture of **23a** (1.19 g, 3.0 mmol), **6** (880 mg, 3.0 mmol), HOBT (410 mg, 3.0 mmol), and THF (20 mL) was treated with DCC (660 mg, 3.2 mmol) and stirred for 24 h. The mixture was filtered, the filtrate concentrated and the residue purified by flash chromatography (hexanes:EtOAc 50:50) to provide the amide (1.81 g, 89%) as a glass: ^{1}H NMR ($CDCl_3$) δ 8.28 (d, J = 5.1 Hz, 1H), 8.17 (s, 1H), 8.04 (s, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.60 (m, 2H), 7.4−7.25 (m, 6H), 6.98 (m, 2H), 5.88 (bm, 1H), 5.13 (s, 2H), 4.47 (bm, 1H), 4.46 (t, J = 7.2 Hz, 2H), 4.01 (t, J = 7.0 Hz, 2H), 3.87 (m, 2H), 2.31 (m, 2H), 1.48 (s, 9H), 1.43 (s, 9H); HRMS (NH_3-CI) m/z 673.3324 [(M + H)$^+$ calcd for $C_{36}H_{44}N_6O_7$ 673.3350]. This material (32 mg, 47 μmol) was dissolved in CH_2Cl_2 (5 mL) and TFA (300 μL) and stirred for 16 h. The solution was concentrated and the residue was triturated with ether to provide **24d** (25 mg, 83%) as a hygroscopic white solid: ^{1}H NMR (MeOH-d_4) δ 8.23 (s, 1H), 8.14 (s, 1H), 7.8 (m, 2H), 7.72 (d, J = 5.5 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.3−7.2 (m, 5H), 6.91 (d, J = 9.2 Hz, 1H), 6.80 (t, J = 7.0 Hz, 1H), 5.02 (ab, J = 12.5 Hz, 2H), 4.58 (t, J = 6.6 Hz, 2H), 4.50 (dd, J = 8.1, 4.9 Hz, 1H), 3.86 (dd, J = 13.7, 4.9 Hz, 1H), 3.71 (dd, J = 13.7, 8.1 Hz, 1H), 3.30 (t, J = 6.6 Hz, 2H), 2.30 (m, 2H); HRMS (FAB) m/z 517.2213 [(M + H)$^+$ calcd for $C_{27}H_{29}N_6O_5$ 517.2199]. Anal. ($C_{27}H_{28}N_6O_5$·1.1CF_3COOH) C, H, N.

3-[*N*-Methyl-*N*-[1-[3-(*N*-pyridin-2-ylamino)propyl]indazol-5-ylcarbonyl]amino]-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)propionic Acid Trifluoroacetate (24b). **23a** (61 mg, 153 μmol) and **9** (48 mg, 153 μmol) were coupled using the procedure described for **24d** to give a colorless glass (106 mg, 100%): ^{1}H NMR ($CDCl_3$) δ 8.30 (m, 1H), 8.02 (s, 1H), 7.83 (s, 1H), 7.61 (m, 2H), 7.46 (m, 1H), 7.38 (m, 1H), 6.98 (m, 1H), 6.95 (s, 2H), 6.05 (bm, 1H), 4.47 (t, J = 7.0 Hz, 2H), 4.30

(bm, 1H), 4.01 (t, J = 7.0 Hz, 2H), 3.97 (bm, 1H), 3.73 (dd, J = 13.6, 4.8 Hz, 1H), 3.54 (s, 3H), 3.10 (s, 3H), 2.66 (s, 6H), 2.31 (m, 2H), 2.28 (s, 3H), 1.43 (s, 9H); HRMS (FAB) *m/z* 693.3045 [(M + H)$^+$ calcd for $C_{35}H_{45}N_6O_7S$ 693.3070]. This material was dissolved in THF (1.5 mL) and water (1.5 mL) and treated with LiOH (1.0 M; 160 μL, 160 μmol). After 19 h, HCl (1.0 M; 160 μL) was added and the mixture was concentrated. The residue was stirred in CH_2Cl_2 (2 mL) with trifluoroacetic acid (2 mL) for 4.5 h. The mixture was concentrated and purifed by HPLC to provide **24b** (65 mg, 74%) as a white powder after lyophilization: ^{1}H NMR (DMSO-d_6) δ 8.78 (bm, 1H), 8.22 (bm, 1H), 8.18 (s, 1H), 7.87 (m, 2H), 7.70 (m, 2H), 7.31 (d, J = 10.3 Hz, 1H), 7.02 (m, 1H), 7.00 (s, 2H), 6.84 (t, J = 6.6 Hz, 1H), 4.56 (t, J = 6.6 Hz, 2H), 4.19 (m, 1H), 3.93 (m, 1H), 3.35 (m, 1H), 3.28 (m, 2H), 2.92 (s, 3H), 2.58 (s, 6H), 2.23 (s, 3H), 2.19 (m, 2H); HRMS (FAB) *m/z* 579.2392 [(M + H)$^+$ calcd for $C_{29}H_{35}N_6O_5S$ 579.2390]. Anal. ($C_{29}H_{34}N_6O_5S\cdot 2.2CF_3COOH$) C, H, N.

Using the procedures described for preparing **24d**, the following compounds were prepared from **23a**.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]propionic acid trifluoroacetate (24c): from β-alanine *tert*-butyl ester, as as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.24 (s, 1H), 8.14 (s, 1H), 7.83 (m, 2H), 7.73 (d, J = 5.5 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 9.2 Hz, 1H), 6.82 (t, J = 6.6 Hz, 1H), 4.57 (t, J = 6.6 Hz, 2H), 3.63 (t, J = 6.6 Hz, 2H), 3.30 (m, 2H), 2.57 (t, J = 7.0 Hz, 2H), 2.30 (m, 2H); HRMS (FAB) *m/z* 368.1721 [(M + H)$^+$ calcd for $C_{19}H_{22}N_5O_3$ 368.1722]. Anal. ($C_{19}H_{21}N_5O_3\cdot 2.6CF_3COOH\cdot 1.3CH_3CN$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-3(*S*)-(2-phenylethylaminocarbonyl)propionic acid trifluoroacetate (24e): from (*S*)-aspartic acid 1-phenethylamide 4-*tert*-butyl ester, as as an amorphous white solid; ^{1}H NMR (DMSO-d_6) δ 8.37 (s, 1H), 8.27 (s, 1H), 8.00 (m, 1H), 7.89 (m, 1H), 7.82 (m, 1H), 7.75 (m, 1H), 7.20 (m, 5H), 6.95 (d, J = 8.8 Hz, 1H), 6.80 (t, J = 6.6 Hz, 1H), 4.79 (m, 1H), 4.57 (t, J = 6.6 Hz, 2H), 2.7 (m, 4H), 2.18 (m, 2H); MS (ESI) *m/z* 515.4 (100%, M + H)$^+$; HRMS (FAB) *m/z* 515.2433 [(M + H)$^+$ calcd for $C_{28}H_{31}N_6O_4$ 515.2406]. Anal. ($C_{28}H_{30}N_6O_4\cdot 1.43CF_3COOH\cdot 2.5CH_3CN$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-3(*S*)-(2,4,6-trimethylphenylaminocarbonyl)-propionic acid trifluoroacetate (24f): from (*S*)-aspartic acid 1-(2,4,6-trimethylphenylamide) 4-*tert*-butyl ester, as as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.31 (s, 1H), 8.16 (s, 1H), 7.83 (m, 2H), 7.71 (d, J = 6.2 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 6.94 (m, 3H), 6.80 (t, J = 6.3 Hz, 1H), 4.79 (t, J = 6.2 Hz, 2H), 4.56 (t, J = 6.6, 2H), 3.28 (m, 2H), 3.26 (m, 2H), 2.27 (m, 8H), 2.06 (s, 3H); HRMS (FAB) *m/z* 529.2551 [(M + H)$^+$ calcd for $C_{29}H_{33}N_6O_4$ 529.2563]. Anal. ($C_{29}H_{32}N_6O_4\cdot 1.2CF_3COOH$) C, H, N.

Ethyl 1-(3-Benzyloxycarbonylaminopropyl)indazole-5-carboxylate (25). A solution of **21** (5.0 g, 18 mmol) and Et_3N (7.5 mL, 19 mmol) in CH_2Cl_2 (100 mL) was cooled on ice, treated with benzyl chloroformate (2.7 mL, 19 mmol), and stirred for 16 h. After concentration, the residue was dissolved in CH_2Cl_2, washed with water, dried, and concentrated to provide **25** (3.4 g, 49%) as a white solid. While this material was suitable for further use, it could be purified by flash chromatography (CH_2Cl_2:MeOH 95:5): ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1H), 8.06 (m, 2H), 7.38 (m, 6H), 5.20 (bm, 1H), 5.02 (s, 2H), 4.42 (m, 4H), 3.18 (m, 2H), 2.18 (m, 2H), 1.40 (t, J = 7.2 Hz, 3H); MS (ESI) *m/z* 382.5 [(M + H)$^+$, 100%].

***tert*-Butyl 3-(1-[3-Benzyloxycarbonylaminopropyl]-indazol-5-ylcarbonylamino)-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)propionate (27). 25** (3.08 g, 8.07 mmol) was dissolved in EtOH (160 mL) and water (40 mL) and treated with LiOH (678 mg, 16.2 mmol). THF was added until the mixture was homogeneous, then stirring was continued for 5 days. After concentration, the residue was taken up in water and washed with EtOAc, and the aqueous phase was acidified to pH 4−5 with aqueous HCl (1.0 M). The resulting mixture was extracted with EtOAc, and the organic phase was dried and concentrated to provide **26** (1.6 g, 56%) as a sticky solid: ^{1}H NMR (DMSO-d_6) δ 8.44 (s, 1H), 8.25 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.72 (d, J = 8.8 Hz, 1H), 7.35 (m, 5H), 5.00 (s, 2H), 4.46 (t, J = 7.0 Hz, 2H), 3.01 (q, J = 7.0 Hz, 2H), 1.98 (m, 2H). This acid (100 mg, 283 μmol) was coupled with **8** (R = *tert*-butyl, Ar = mesityl) (107 mg, 283 μmol) using DCC as described for the preparation of **24d** to give **27** (130 mg, 68%) as a yellowish solid: ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 1H), 8.09 (s, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.36 (m, 5H), 6.93 (s, 2H), 6.83 (m, 1H), 5.78 (d, J = 7.3 Hz, 1H), 5.09 (s, 2H), 4.47 (t, J = 6.6 Hz, 2H), 4.02 (m, 1H), 3.84 (m, 1H), 3.62 (m, 1H), 3.46 (m, 1H), 3.18 (m, 2H), 2.66 (s, 6H), 2.26 (s, 3H), 2.15 (m, 2H), 1.21 (s, 9H); MS (ESI) *m/z* 678.4 [(M + H)$^+$, 100%].

***tert*-Butyl 3-(1-[3-Aminopropyl]indazol-5-ylcarbonylamino)-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)propionate (28).** A mixture of **27** (50 mg, 74 μmol), $Pd(OH)_2$ on charcoal (15 mg), 1,4-cyclohexadiene (1 mL), and MeOH (2 mL) was heated at reflux for 4 h. The mixture was cooled and filtered through Celite, and the solids were rinsed with MeOH. The filtrate was concentrated to provide **28** (34 mg, 85%) as a solid which was used without purification: ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.80−7.65 (m, 3H), 7.31 (d, J = 8.8 Hz, 1H), 6.84 (s,H), 4.40 (m, 2H), 4.02 (m, 1H), 3.78 (m, 2H), 3.06 (m, 2H), 2.63 (m, 1H), 2.59 (s, 6H), 2.27 (m, 2H), 2.19 (s, 3H), 1.23 (s, 9H); MS (ESI) *m/z* 544.5 [(M + H)$^+$, 100%].

3-[1-[3-(*N*-4,5-Dihydroimidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)propionic Acid Trifluoroacetate (29a). A mixture of **28** (60 mg, 110 μmol), 2-methylthio-4,5-dihydroimidazole hydroiodide (32 mg, 130 μmol), and pyridine (5 mL) was heated at 120 °C for 18 h. After concentration, the residue was purified by flash chromatography (CH_2Cl_2:MeOH 90:10), deprotected by treatment with TFA (1 mL) and CH_2Cl_2 (2 mL), and purified by HPLC to provide **29a** (15 mg, 22%) as an amorphous white solid: ^{1}H NMR (MeOH-d_4) δ 8.18 (s, 2H), 7.80 (d, J = 8.8, 1.5 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 6.79 (s, 2H), 4.54 (t, J = 6.6 Hz, 2H), 4.16 (dd, J = 9.2, 4.8 Hz, 1H), 3.78 (dd, J = 13.6, 4.8 Hz, 1H), 3.60 (s, 4H), 3.48 (dd, J = 13.6, 9.2 Hz, 1H), 3.18 (t, J = 6.6 Hz, 2H), 2.58 (s, 6H), 2.25 (m, 2H), 2.02 (s, 3H); HRMS (FAB) *m/z* 556.2343 [(M + H)$^+$ calcd for $C_{26}H_{34}N_7O_5S$ 556.2342]. Anal. ($C_{26}H_{33}N_7O_5S\cdot 0.9CF_3COOH\cdot 0.8H_2O$) C, H, N.

3-[1-[3-(*N*-(3,4,5,6-Tetrahydropyrimidin-2-yl)amino)-propyl]indazol-5-ylcarbonylamino]-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)propionic Acid Trifluoroacetate (29b). Using the same procedure, **28** and 2-methylthio-3,4,5,6-tetrahydropyrimidine hydroiodide were converted to **29b** as an amorphous solid after HPLC purification: ^{1}H NMR (DMSO-d_6) δ 8.47 (m, 1H), 8.25 (s, 1H), 8.19 (s, 1H), 8.06 (d, J = 9.5 Hz, 2H), 7.80 (d, J = 9.5 Hz, 2H), 7.32 (m, 1H), 6.84 (s, 1H), 4.47 (t, J = 13.6 Hz, 2H), 4.02 (dd, J = 9.2, 4.8 Hz, 1H), 3.58 (m, 2H), 3.20 (m, 4H), 3.03 (m, 2H), 2.55 (s, 6H), 2.17 (s, 3H), 2.07 (m, 2H), 1.78 (m, 2H); HRMS (FAB) *m/z* 570.2509 [(M + H)$^+$ calcd for $C_{27}H_{36}N_7O_5S$ 570.2498]. Anal. ($C_{27}H_{36}N_7O_5S\cdot 2.3CF_3COOH\cdot H_2O$) C, H, N.

Ethyl 1-[2-(1,3-Dioxolan-2-yl)ethyl]indazole-5-carboxylate (30). A solution of **12a** (74.5 g, 397 mmol) in THF (1000 mL) was treated with sodium bis(trimethylsilyl)amide (1.0 M in THF; 430 mL, 430 mmol), 18-crown-6 (1.5 g), and 2-(2-bromoethyl)-1,3-dioxolane (90 g, 496 mmol). The solution was heated at reflux for 20 h, cooled, and concentrated. The residue was partitioned between toluene and water. The aqueous phase was further extracted with toluene, and the combined organic phases were washed with water and brine, then dried and concentrated. The resulting oil was chromatographed (toluene, then 185:15 toluene−EtOAc) to provide **30** (71.0 g, 55%): ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H), 8.10 (s, 1H), 8.06 (d, J = 9.2 Hz, 1H), 7.46 (d, J = 9.2 Hz, 1H), 4.84 (t, J = 4.4 Hz, 1H), 4.55 (t, J = 7.0 Hz, 2H), 4.41 (q, J = 7.0 Hz, 2H), 3.90 (m, 4H), 2.31 (m, 2H), 1.42 (t, J = 7.0 Hz, 3H); HRMS (NH_3-CI) *m/z* 291.1328 [(M + H)$^+$ calcd for $C_{15}H_{19}N_2O_4$ 291.1345].

Ethyl 1-[3-Oxopropyl]indazole-5-carboxylate (31). A mixture of **30** (73.0 g, 256 mmol), HOAc (365 g), and water (1020 mL) was heated at 70 °C for 20 h, cooled, and extracted

with CH_2Cl_2 (5 × 500 mL). The extract was washed cautiously with aqueous $NaHCO_3$ until no more gas was evolved, then with water and brine, then was dried and concentrated to give **31** (60.9 g, 98%) as a light yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.87 (s, 1H), 8.50 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 8.10 (s, 1H), 7.51 (d, J = 8.8 Hz, 1H), 4.70 (t, J = 6.2 Hz, 2H), 4.41 (q, J = 7.2 Hz, 2H), 3.19 (t, J = 6.2 Hz, 2H), 1.42 (t, J = 7.2 Hz, 3H); HRMS (NH_3-CI) m/z 247.1068 [$(M + H)^+$ calcd for $C_{13}H_{15}N_2O_3$ 247.1083].

Ethyl 1-[3-(*N*-(1-Triphenylmethylimidazol-2-ylamino)-propyl]indazole-5-carboxylate (32a). A mixture of **31** (10.0 g, 40.6 mmol), 1-triphenylmethyl-2-aminoimidazole[22] (13.2 g, 40.6 mmol), and toluene (500 mL) was heated at reflux under a Dean−Stark trap. Toluene (300 mL) was removed while adding an equivalent amount; the mixture was then heated further for 20 h, when NMR analysis of an aliquot showed the absence of aldehyde. The mixture was cooled, $NaBH(OAc)_3$ (34.42 g, 162.4 mmol) was added, stirring was continued for 20 h, and the reaction was poured into water. The layers were separated and the aqueous phase was extracted with EtOAc. The combined extracts were washed with aqueous $NaHCO_3$, water, and brine, then were dried and concentrated to provide a crude product (25.0 g). This was purified by flash chromatography (toluene:EtOAc, step gradient from 90:10 to 50:50) to provide **32a** (11.2 g, 52%) as an oil which slowly solidified: ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 7.97 (s, 1H), 7.93 (d, J = 8.8 Hz, 1H), 7.33 (m, 9H), 7.21 (m, 6H), 6.99 (d, J = 8.8 Hz, 1H), 6.67 (d, J = 1.8 Hz, 1H), 6.41 (d, J = 1.8 Hz, 1H), 4.41 (q, J = 7.2 Hz, 2H), 4.06 (t, J = 6.6 Hz, 2H), 2.98 (m, 3H), 1.81 (m, 2H), 1.42 (t, J = 7.2 Hz, 3H); HRMS (FAB) m/z 556.2725 [(M + H)$^+$ calcd for $C_{35}H_{34}N_5O_2$ 556.2713].

1-[3-(*N*-(1-Triphenylmethylimidazol-2-yl)amino)propyl]-indazole-5-carboxylic Acid (33a). A mixture of **32a** (10.5 g, 18.9 mmol), EtOH (300 mL), and aqueous NaOH (1.0 M; 105 mL, 105 mmol) was heated at reflux for 4 h. The solution was cooled and concentrated to remove the EtOH. The pH of the aqueous residue was adjusted to 4, the mixture was extracted with CH_2Cl_2, and the organic phases were dried (Na_2SO_4). The mixture was filtered and the solids were washed with DMF to recover precipitated product. The combined filtrates were concentrated, and the residue was washed with EtOH and dried to provide **33a** (8.5 g, 85%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 8.39 (s, 1H), 8.13 (s, 1H), 7.87 (d, J = 8.8 Hz, 1H), 7.36 (m, 10H), 7.12 (d, J = 8.8 Hz, 6H), 6.51 (d, J = 1.8 Hz, 1H), 6.28 (d, J = 1.8 Hz, 1H), 4.05 (t, J = 6.7 Hz, 2H), 2.84 (m, 2H), 1.63 (m, 2H); HRMS (FAB) m/z 528.2418 [(M + H)$^+$ calcd for $C_{33}H_{30}N_5O_2$ 528.2400]. Anal. ($C_{33}H_{29}N_5O_2\cdot 0.2H_2O$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)-propionic Acid Trifluoroacetate (34a). A solution of **33a** (215 mg, 407 μmol), **8** (R = *tert*-butyl, Ar = mesityl) (140 mg, 407 μmol), DCC (87 mg, 407 μmol), and HOBT (57 mg, 407 μmol) in DMF (5 mL) was stirred for 24 h and poured into water. The mixture was extracted with EtOAc, and the extract was dried and concentrated. Purification by flash chromatography (toluene:EtOAc 70:30) provided the coupled product (261 mg, 75%) as a soft solid: ^{1}H NMR ($CDCl_3$) δ 8.17 (s, 1H), 7.97 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.4−7.1 (15H), 6.99 (d, J = 8.8 Hz, 1H), 6.94 (s, 2H), 6.85 (bm, 1H), 6.68 (d, J = 1.8 Hz, 1H), 6.42 (d, J = 1.8 Hz, 1H), 5.82 (bm, 1H), 4.07 (t, J = 7.0 Hz, 2H), 3.93 (m, 1H), 3.83 (m, 1H), 3.62 (m, 1H), 3.04 (m, 1H), 2.97 (m, 2H), 2.65 (s, 6H), 2.26 (s, 3H), 1.82 (m, 2H), 1.32 (s, 9H); MS (ESI) m/z 852.4 [(M + H)$^+$,100%]. A solution of this material (250 mg, 294 μmol) in MeOH (8 mL) and HOAc (1 mL) was heated at reflux overnight, cooled, and concentrated. The residue was flash chromatographed ($CHCl_3$:MeOH: aqueous NH_3 90:10:1) to provide the detritylated product (145 mg, 81%) as a glassy foam: ^{1}H NMR (MeOH-d_4) δ 8.17 (s, 1H), 8.13 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 6.85 (s, 2H), 6.51 (s, 2H), 4.53 (t, J = 7.0 Hz, 2H), 4.06 (m, 1H), 3.70 (m, 1H), 3.50 (m, 1H), 3.17 (t, J = 7.0 Hz, 2H), 2.59 (s, 6H), 2.16 (m, 2H), 2.10 (s, 3H), 1.22 (s, 9H). A solution of this material (135 mg, 222 μmol) in CH_2Cl_2 (6 mL) and TFA (1 mL) was stirred for 1 h, concentrated, and purified by HPLC to provide **34a** (121 mg, 82%) as an amorphous white solid after lyophilization: ^{1}H NMR (MeOH-d_4) δ 8.12 (s, 2H), 7.72 (dd, J = 8.8, 1.5 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 6.76 (s, 2H), 6.73 (s, 2H), 4.53 (t, J = 6.6 Hz, 2H), 4.16 (dd, J = 9.2, 4.8 Hz, 1H), 3.76 (dd, J = 13.6, 4.8 Hz, 1H), 3.49 (dd, J = 13.6, 9.2 Hz, 1H), 3.23 (t, J = 6.6 Hz, 2H), 2.56 (s, 6H), 2.22 (m, 2H), 1.98 (s, 3H); HRMS (FAB) m/z 554.2196 [(M + H)$^+$ calcd for $C_{26}H_{32}N_7O_5S$ 554.2186]. Anal. ($C_{26}H_{31}N_7O_5S\cdot 0.9CF_3COOH$) C, H, N, S, F.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-4-ylcarbonylamino]-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)-propionic Acid Trifluoroacetate (34b). This compound was prepared as described for **33a** and **34a** from **12c** as an amorphous white solid: ^{1}H NMR (MeOH-d_4) δ 8.36 (m, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.37 (m, 2H), 6.75 (s, 2H), 6.72 (s, 2H), 4.52 (t, J = 6.2 Hz, 2H), 4.20 (m, 1H), 3.80 (dd, J = 13.5, 4.7 Hz, 1H), 3.52 (dd, J = 13.5, 9.1 Hz, 1H), 3.21 (t, J = 6.6 Hz, 2H), 2.55 (s, 6H), 2.19 (m, 2H), 2.04 (s, 3H); HRMS (FAB) m/z 554.2192 [(M + H)$^+$ calcd for $C_{26}H_{32}N_7O_5S$ 554.2185]. Anal. ($C_{26}H_{31}N_7O_5S\cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)propionic Acid Trifluoroacetate (34c). This compound was prepared by coupling **33a** and **6** as described for the preparation of **34a**. Both the trityl and *tert*-butyl protecting groups were removed by heating at reflux in TFA for 4 h, followed by concentration and purification by HPLC, to provide **34c** in 45% overall yield as an amorphous white solid: ^{1}H NMR (MeOH-d_4) δ 8.23 (s, 1H), 8.22 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 7.23 (m, 5H), 6.76 (s, 2H), 5.02 (m, 2H), 4.52 (m, 3H), 3.86 (dd, J = 13.6, 4.8 Hz, 1H), 3.72 (dd, J = 13.9, 8.0 Hz, 1H), 3.22 (t, J = 13.9 Hz, 2H), 2.1 (m, 2H); HRMS (FAB) m/z 506.2166 [(M + H)$^+$ calcd for $C_{25}H_{28}N_7O_5$ 506.2152]. Anal. ($C_{25}H_{27}N_7O_5\cdot 1.2CF_3COOH\cdot 1.5H_2O$) C, H, N.

Using the procedures described for preparing **34a** and **34c**, the following compounds were prepared from **33a**.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*R*)-(2,4,6-trimethylbenzenesulfonylamino)-propionic acid trifluoroacetate (34d): from the enantiomer of **8** (R = *tert*-butyl, Ar = mesityl), as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.14 (m, 2H), 7.75 (d, J = 9.1 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 6.77 (m, 4H), 4.55 (t, J = 6.3 Hz, 2H), 4.18 (m, 1H), 3.75 (dd, J = 13.6, 4.8 Hz, 1H), 3.48 (dd, J = 13.5, 9.1 Hz, 1H), 3.23 (t, J = 6.6 Hz, 2H), 2.57 (s, 6H), 2.23 (m, 2H) 2.01 (s, 3H); HRMS (FAB) m/z 554.2191 [(M + H)$^+$ calcd for $C_{26}H_{32}N_7O_5S$ 554.2186]. Anal. ($C_{26}H_{31}N_7O_5S\cdot CF_3$-COOH) C, H, N.

***N*-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonyl]-*N*′-(2,4,6-trimethylbenzenesulfonyl)ethylenediamine trifluoroacetate (34e)**: from **51**, as a white powder; ^{1}H NMR (MeOH-d_4) δ 8.22 (s, 1H), 8.16 (s, 1H), 7.82 (d, J = 9.2 Hz, 1H), 7.59 (d, J = 9.2 Hz, 1H), 6.91 (s, 2H), 6.80 (s, 2H), 4.56 (m, 2H), 3.43 (m, 2H), 3.24 (m, 2H), 3.08 (m, 2H), 2.59 (s, 6H), 2.24 (m, 2 H), 2.17 (s, 3H); HRMS (FAB) m/z 510.2310 [(M + H)$^+$ calcd for $C_{25}H_{32}N_7O_3S$ 510.2287]. Anal. ($C_{25}H_{31}N_7O_3S\cdot 1.2CF_3COOH$) C, H, N, S, F.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]propionic acid trifluoroacetate (34f): from β-alanine *tert*-butyl ester, as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.26 (s, 1H), 8.15 (s, 1H), 7.84 (d, J = 8.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H), 6.78 (s, 2H), 4.55 (t, J = 6.6 Hz, 2H), 3.63 (t, J = 6.6 Hz, 2H), 3.23 (t, J = 6.6 Hz, 2H), 2.64 (t, J = 6.6 Hz, 2H), 2.23 (m, 2H); HRMS (FAB) m/z 357.1683 [(M + H)$^+$ calcd for $C_{17}H_{21}N_6O_3$ 357.1675]. Anal. ($C_{17}H_{20}N_6O_3\cdot 1.06CF_3COOH$) C, H, F; N: calcd, 17.61; found, 17.15.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)- (benzenesulfonylamino)propionic acid trifluoroacetate (34g): from **8** (R = *tert*-butyl, Ar = phenyl), as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.21 (s, 1H), 8.15 (s, 1H), 7.80 (m, 3H), 7.56 (d, J = 9.2 Hz, 1H), 7.40 (m, 3H), 4.55 (t, J = 6.6 Hz, 2H), 4.23 (m, 1H), 3.77 (dd, J = 13.5, 5.1 Hz, 1H), 3.50 (dd, J = 13.6, 8.8 Hz, 1H), 3.21 (t, J = 6.6 Hz, 2H), 2.23 (m, 2H); HRMS (FAB) m/z 512.1718 [(M +

H)$^+$ calcd for $C_{23}H_{27}N_7O_5S$ 512.1716]. Anal. ($C_{23}H_{26}N_7O_5S\cdot 1.1CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(4-phenylbenzenesulfonylamino)propionic acid trifluoroacetate (34p): from **8** (R = methyl, Ar = 4-biphenyl), as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.14 (s, 1H), 8.06 (s, 1H), 7.83 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.7 Hz, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.34 (m, 6H), 6.77 (s, 2H), 4.42 (t, J = 6.6 Hz, 2H), 4.29 (m, 1H), 3.79 (dd, J = 13.5, 4.4 Hz, 1H), 3.49 (dd, J = 13.5, 9.1 Hz, 1H), 3.19 (t, J = 6.5 Hz, 2H), 2.16 (m, 2H); HRMS (FAB) m/z 588.2026 [(M + H)$^+$ calcd for $C_{29}H_{30}N_7O_5S$ 588.2029]. Anal. ($C_{29}H_{29}N_7O_5S\cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(2,6-dichlorobenzenesulfonylamino)-propionic acid trifluoroacetate (34r): from **8** (R = methyl, Ar = 2,6-dichlorophenyl), as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.20 (s, 1H), 8.15 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 7.7 Hz, 1H), 7.22 (m, 1H), 6.76 (s, 1H), 4.56 (t, J = 6.6 Hz, 2H), 4.42 (m, 1H), 3.84 (dd, J = 13.5, 4.4 Hz, 1H), 3.58 (dd, J = 14.0, 9.2 Hz, 1H), 3.21 (t, J = 6.6 Hz, 2H), 2.34 (m, 2H); HRMS (FAB) m/z 580.0935 [(M + H)$^+$ calcd for $C_{23}H_{24}Cl_2N_7O_5S$ 580.0937]. Anal. ($C_{23}H_{23}Cl_2N_7O_5S\cdot CF_3COOH\cdot 0.5CH_3CN$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(2,6-dimethylbenzenesulfonylamino)-propionic acid trifluoroacetate (34s): from **8** (R = methyl, Ar = 2,6-dimethylphenyl), as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.12 (s, 1H), 8.11 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 6.96 (d, J = 7.7 Hz, 2H), 6.75 (s, 2H), 4.52 (t, J = 6.6 Hz, 2H), 4.17 (m, 1H), 3.76 (dd, J = 13.6, 4.8 Hz, 1H), 3.52 (dd, J = 13.5, 8.7 Hz, 1H), 3.21 (t, J = 6.6 Hz, 2H), 2.60 (s, 6H), 2.21 (m, 2H); HRMS (FAB) m/z 540.2024 [(M + H)$^+$ calcd for $C_{25}H_{33}N_6O_4S$ 540.2029]. Anal. ($C_{25}H_{32}N_6O_4S\cdot 1.43CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(4-phenyl-2,6-dimethylbenzenesulfonylamino)propionic acid trifluoroacetate (34t): from **8** (R = *tert*-butyl, Ar = 4-phenyl-2,6-dimethylphenyl), as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.06 (s, 1H), 7.95 (s, 1H), 7.63 (d, J = 9.1 Hz, 2H), 7.29 (m, 6H), 7.10 (s, 2H), 4.34 (t, J = 6.3 Hz, 2H), 4.27 (m, 1H), 3.77 (dd, J = 13.5, 4.4 Hz, 1H), 3.50 (dd, J = 13.51, 9.9 Hz, 1H), 3.17 (t, J = 6.6 Hz, 2H), 2.66 (s, 6H), 2.11 (m, 2H); HRMS (FAB) m/z 616.2323 [(M + H)$^+$ calcd for $C_{31}H_{34}N_7O_5S$ 616.2342]. Anal. ($C_{31}H_{33}N_7O_5S\cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(1-naphthalenesulfonylamino)propionic Acid Trifluoroacetate (34u). 33a was coupled with **8** (R = methyl, Ar = 1-naphthyl) as described for the synthesis of **34a**. A solution of this product (216 mg, 260 μmol) in EtOH (7 mL) was treated with NaOH (1.0 N; 1.3 mL, 1.3 mmol) and heated at reflux for 5 h. The solution was cooled, treated with aqueous HCl (1.0 N, 1.5 mL), and concentrated. The residue was heated at reflux in TFA (2.5 mL) for 1.5 h, then concentrated and purified by HPLC to provide **34u** (118 mg, 67%) as an amorphous white solid: ^{1}H NMR (MeOH-d_4) δ 8.63 (d, J = 8.8 Hz, 1H), 8.15 (d, J = 7.3 Hz, 1H), 8.07 (s, 1H), 7.85 (m, 2H), 7.63 (d, J = 8.1 Hz, 1H), 7.54 (m, 2H), 7.32−7.45 (3H), 6.76 (s, 2H), 4.52 (t, J = 6.6 Hz, 2H), 4.22 (m, 1H), 3.50 (dd, J = 13.6, 4.8 Hz, 1H), 3.22 (dd, J = 13.6, 9.2 Hz, 1H), 3.22 (t, J = 6.6 Hz, 2H), 2.21 (m, 2H); HRMS (FAB) m/z 562.1860 [(M + H)$^+$ calcd for $C_{27}H_{28}N_7O_5S$ 562.1872]. Anal. ($C_{27}H_{27}N_7O_5S\cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Pyrazol-3-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)-propionic Acid Trifluoroacetate (35). A solution of 1-Cbz-3-aminopyrazole[37] (282 mg, 1.3 mmol) and **31** (246 mg, 1.0 mmol) in 1,2-dichloroethane (5 mL) was treated with $NaBH(OAc)_3$ (424 mg, 2.0 mmol). After 21 h, the mixture was treated with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was dried and concentrated, and the residue was purified by flash chromatography (toluene:EtOAc 60:40) to provide **32b** (249 mg, 56%) as a pale yellow glass: ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.10 (s, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 2.9 Hz, 1H), 7.5−7.3 (m, 6H), 5.73 (d, J = 2.9 Hz, 1H), 5.39 (s, 2H), 4.52 (t, J = 6.2 Hz, 2H), 4.41 (q, J = 7.0 Hz, 2H), 4.26 (bm, 1H), 3.24 (q, J = 6.4 Hz, 2H), 2.23 (m, 2H), 1.43 (t, J = 6.4 Hz, 3H); HRMS (FAB) m/z 448.1971 [(M + H)$^+$ calcd for $C_{24}H_{26}N_5O_4$ 448.1985]. A solution of **32b** (217 mg, 485 μmol) in EtOH (2.5 mL) was treated with LiOH (1.0 N; 1.5 mL, 1.5 mmol). After 22 h, HCl (1.0 N, 1.5 mL) was added and the mixture was concentrated. The residue was coupled with **8** (R = *tert*-butyl, Ar = 2,4,6-trimethylphenyl) according to the method for the preparation of **34a** to give the product (111 mg, 38%) as a glassy foam: ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1H), 8.08 (s, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 2.6 Hz, 1H), 6.93 (s, 2H), 7.0−6.9 (m, 2H), 6.06 (bs, 1H), 5.56 (d, J = 2.2 Hz, 1H), 4.53 (t, J = 6.6 Hz, 2H), 4.0−3.6 (m, 4H), 3.15 (t, J = 6.6 Hz, 2H), 2.65 (s, 6H), 2.26 (s, 3H), 2.23 (m, 2H), 1.30 (s, 9H); HRMS (FAB) m/z 610.2824 [(M + H)$^+$ calcd for $C_{30}H_{40}N_7O_5S$ 610.2812]. This material (95 mg, 156 μmol) was deprotected with TFA (3 mL) in CH_2Cl_2 (3 mL) for 6 h and purified by HPLC to provide **35** (54 mg, 54%) as a white solid after lyophilization: ^{1}H NMR (DMSO-d_6) δ 8.44 (t, J = 5.7 Hz, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 8.06 (d, J = 9.5 Hz, 1H), 7.80 (s, 1H), 7.76 (d, J = 8.8 Hz, 1H), 7.69 (d, J = 8.8 Hz, 1H), 6.82 (s, 2H), 4.53 (t, J = 7 Hz, 2H), 4.01 (m, 1H), 3.57 (m, 1H), 3.40 (m, 1H), 3.10 (t, J = 7 Hz, 2H), 2.53 (s, 6H), 2.10 (m, 2H), 2.05 (s, 3H); HRMS (FAB) m/z 554.2192 [(M + H)$^+$ calcd for $C_{26}H_{32}N_7O_5S$ 554.2186]. Anal. ($C_{26}H_{31}N_7O_5S\cdot 1.4CF_3COOH$) C, H, N, S, F.

Ethyl 1-(2-Methoxycarbonylethyl)indazole-5-carboxylate (36). A solution of **12a** (3.80 g, 20 mmol), methyl acrylate (1.8 mL, 20 mmol), and tBuOH (1.91 mL, 20 mmol) in THF (400 mL) was treated with KOtBu (1.0 M in THF; 1.0 mL, 1.0 mmol), heated at reflux for 45 min, cooled, treated with HCl (1.0 N; 2 mL), and concentrated to provide crude **36** (5.40 g, 97%) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 8.51 (s, 1H), 8.10 (s, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.51 (d, J = 9.2 Hz, 1H), 4.68 (t, J = 6.6 Hz, 2H), 4.41 (q, J = 7.3 Hz, 2H), 3.63 (s, 3H), 3.01 (t, J = 6.6 Hz, 2H), 1.42 (t, J = 7.3 Hz, 3H); MS (NH_3-CI) m/z 277.2 [(M + H)$^+$, 100%].

Ethyl 1-(2-Carboxyethyl)indazole-5-carboxylate (37). A solution of **36** (1.00 g, 3.62 mmol) in THF (7 mL) was treated with a solution of LiOH (304 mg, 7.24 mmol) in water (7 mL) and stirred vigorously for 5 min. HCl (1.0 N, 8 mL) was added, followed by additional water (10 mL). The THF was removed under vacuum and the resulting solid was isolated by filtration to give **37** (820 mg, 86%) as an off-white solid: mp 102−110 °C; ^{1}H NMR ($CDCl_3$) δ 8.50 (s, 1H), 8.12 (s, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.48 (d, J = 9.2 Hz, 1H), 4.67 (t, J = 6.6 Hz, 2H), 4.41 (q, J = 7.0 Hz, 2H), 3.05 (t, J = 6.6 Hz, 2H), 1.41 (t, J = 7.0 Hz, 3H); MS (NH_3-CI) m/z 191.2 [(M + H − acrylic acid)$^+$, 100%]. Anal. ($C_{13}H_{14}N_2O_4$) C, H, N.

Ethyl 1-(2-[*N*-Imidazol-2-ylaminocarbonyl]ethyl)indazole-5-carboxyate (38). A mixture of **37** (352 mg, 1.34 mmol), 2-aminoimidazole sulfate (0.55 g, 4.15 mmol), iPr_2NEt (1.17 mL, 6.7 mL), and DMF (7 mL) was treated with BOP reagent (891 mg, 2.0 mmol) and warmed to 70 °C. After 18 h the mixture was cooled and diluted with water. The resulting precipitate was collected by filtration to provide **38** (310 mg, 71%) which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 8.49 (s, 1H), 8.11 (s, 1H), 8.07 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.8 Hz, 1H), 4.75 (t, J = 7.0 Hz, 2H), 4.41 (q, J = 7.3 Hz, 2H), 3.01 (t, J = 7.0 Hz, 2H), 1.42 (t, J = 7.3 Hz, 3H); HRMS (NH_3-CI) m/z 328.1030 [(M + H)$^+$ calcd for $C_{16}H_{18}N_5O_3$ 328.1046].

3-[1-[2-(*N*-Imidazol-2-ylaminocarbonyl)ethyl]indazol-5-ylcarbonylamino]-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)propionic Acid Trifluoroacetate (39). A solution of **38** (145 mg, 443 μmol) in THF (2 mL) and water (2 mL) was treated with LiOH (1.0 M; 0.56 mL, 560 μmol). After 21 h the reaction was incomplete by TLC so additional LiOH (1.35 mL) was added in four portions over the next 8 h. After 16 h more, the reaction was acidified with HCl (1.0 M) and concentrated. The residue was partitioned between water and CH_2Cl_2, and the organic phase was dried and concentrated to

provide the acid (49 mg, 37%): ^{1}H NMR (DMSO-d_6) δ 8.41 (s, 1H), 8.24 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.76 (d, J = 8.8 Hz, 1H), 6.67 (s, 2H), 4.73 (t, J = 6.6 Hz, 2H), 3.00 (t, J = 6.6 Hz, 2H); HRMS (NH_3-CI) m/z 300.1097 [$(M + H)^+$ calcd for $C_{14}H_{14}N_5O_3$ 300.1097]. This material (48 mg, 160 μmol) was coupled with **8** (R = *tert*-butyl, Ar = 2,4,6-trimethylphenyl) according to the method for the preparation of **34a**, deprotected with TFA in CH_2Cl_2, and purified by HPLC to provide **39** (28 mg, 31%) as an amorphous white solid: ^{1}H NMR (MeOH-d_4) δ 8.11 (s, 1H), 8.09 (s, 1H), 7.77 (d, J = 10.6 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.10 (s, 2H), 6.73 (s, 2H), 4.81 (t, J = 6.2 Hz, 2H), 4.14 (m, 1H), 3.74 (dd, J = 13.6, 4.8 Hz, 1H), 3.46 (dd, J = 13.5, 9.1 Hz, 1H), 3.19 (t, J = 6.3 Hz, 2H), 2.56 (s, 6H), 1.97 (s, 3H); HRMS (FAB) m/z 568.1971 [$(M + H)^+$ calcd for $C_{26}H_{30}N_7O_6S$ 568.1978].

***tert*-Butyl 3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(benzyloxycarbonylamino)-propionate (40a).** A mixture of **22b** (1.2 g, 3.7 mmol), aqueous NaOH (1.0 M; 15 mL, 15 mmol), and EtOH (15 mL) was heated for 24 h at reflux. The pH of the cooled solution was adjusted to ca. 6.5 with aqueous HCl (1.0 M) and the precipitate collected by filtration to provide **23b** as a white solid: ^{1}H NMR (DMSO-d_6) δ 8.44 (s, 1H), 8.25 (s, 1H), 7.93 (m, 1H), 7.91 (d, J = 1.5 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.34 (m, 1H), 6.57 (bt, J = 5.2 Hz, 1H), 6.45 (m, 2H), 4.53 (t, J = 7.0 Hz, 2H), 3.20 (m, 2H), 2.10 (m, 2H). This material (740 mg, 2.5 mmol) was coupled with **6** using the procedure of **24d** to provide **40a** (700 mg, 56%) as a glass: ^{1}H NMR ($CDCl_3$) δ 8.19 (s, 1H), 8.09 (s, 1H), 8.05 (d, J = 5.0 Hz, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.4−7.25 (m, 8H), 7.01 (m, 1H), 6.56 (m, 1H), 6.32 (d, J = 8.4 Hz, 1H), 5.90 (m, 1H), 5.13 (s, 2H), 4.53 (t, J = 6.6 Hz, 2H), 4.05 (m, 1H), 3.85 (m, 2H), 3.28 (m, 2H), 2.26 (m, 2H), 1.48 (s, 9H); MS (FAB) m/z 573 [$(M + H)^+$, 100%].

***tert*-Butyl 3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)- aminopropionate (41a).** A mixture of **40a** (1.60 g, 2.33 mmol), 10% Pd on charcoal (160 mg), and EtOH (30 mL) was stirred under H_2 (1 atm). After 5 h, the mixture was filtered through Celite, the solids were rinsed with EtOH, and the filtrate was concentrated to provide **41a** (1.24 g, 97%) as a glass: ^{1}H NMR ($CDCl_3$) δ 8.28 (m, 1H), 8.19 (s, 1H), 8.06 (s, 1H), 7.82 (d, J = 8.8 Hz, 1H), 7.60 (m, 2H), 7.38 (d, J = 8.8 Hz, 1H), 6.98 (m, 1H), 6.93 (bt, J = 5.1 Hz, 1H), 4.45 (t, J = 7.3 Hz, 2H), 4.00 (t, J = 7.0 Hz, 2H), 3.88 (m, 1H), 3.66 (m, 1H), 3.56 (m, 1H), 2.51 (m, 2H), 1.70 (bs, 2H), 1.48 (s, 9H), 1.42 (s, 9H); HRMS (NH_3-CI) m/z 539.2998 [$(M + H)^+$ calcd for $C_{28}H_{39}N_6O_5$ 539.2982]. Anal. ($C_{28}H_{38}N_6O_5$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(isobutyloxycarbonylamino)propionic Acid Trifluoroacetate (24g). A solution of **41a** (100 mg, 187 μmol), pyridine (15 μL, 205 μmol), and 4-(dimethylamino)pyridine (10 mg, 82 μmol) in DMF (5 mL) was treated with isobutyl chloroformate (27 μL, 205 μmol) and stirred for 18 h. The mixture was concentrated and purified by flash chromatography (hexanes:EtOAc 60:40) to provide **42a** (R = isobutyloxycarbonyl; 106 mg, 89%) as a gum: ^{1}H NMR (DMSO-d_6) δ 8.52 (m, 2H), 8.28 (s, 1H), 8.21 (s, 1H), 7.95 (s, 1H), 7.90−7.65 (3H), 7.53 (d, J = 8.00 Hz, 1H), 7.10 (m, 1H), 6.47 (m, 1H), 4.45 (t, J = 6.6 Hz, 2H), 4.21 (m, 1H), 3.83 (m, 2H), 3.75 (d, J = 7.00 Hz, 2H), 3.70 (m, 1H), 3.58 (m, 1H), 2.14 (m, 2H), 1.83 (m, 1H), 1.33 (s, 9H), 1.30 (s, 9H), 0.88 (d, J = 7.00 Hz, 6H); HRMS (FAB) m/z 639.3506 [$(M + H)^+$ calcd for $C_{33}H_{47}N_6O_7$ 639.3480]. This material (106 mg, 166 μmol) was treated with TFA (1.0 mL) in CH_2Cl_2 (3 mL) to provide **24g** (76 mg, 76%) as an amorphous white solid: ^{1}H NMR (DMSO-d_6) δ 8.56 (m, 2H), 8.30 (s, 1H), 8.25 (s, 1H), 7.89−7.75 (4H), 7.43 (d, J = 8.00 Hz, 1H), 6.95 (d, J = 8.00 Hz, 1H), 6.80 (t, J = 6.2 Hz, 1H), 4.54 (t, J = 6.6 Hz, 2H), 4.16 (m, 1H), 3.78 (d, J = 7.00 Hz, 2H), 3.60 (m, 2H), 3.28 (br, 2H), 3.18 (t, J = 6.6 Hz, 2H), 1.80 (m, 1H), 0.86 (d, J = 7.00 Hz, 6H); HRMS (FAB) m/z 483.2355 [$(M + H)^+$ calcd for $C_{24}H_{31}N_6O_5$ 483.2348]. Anal. ($C_{24}H_{30}N_6O_5 \cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)-propionic Acid Trifluoroacetate (24a). This compound was prepared as described for **24g** from **41a** and mesitylenesulfonyl chloride as a white solid: ^{1}H NMR (DMSO-d_6) δ 8.78 (bs, 1H), 8.44 (bt, 1H), 8.20 (s, 1H), 8.14 (s, 1H), 8.03 (d, J = 9.5 Hz, 1H), 7.88 (d, J = 5.9 Hz, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.70 (m, 2H), 6.96 (d, J = 8.8 Hz, 1H), 6.80 (s, 2H), 4.53 (t, J = 6.4 Hz, 2H), 4.00 (dd, J = 15.3, 7.5 Hz, 1H), 3.52 (m, 1H), 3.38 (m, 1H), 3.28 (m, 2H), 2.49 (s, 6H), 2.15 (m, 2H), 2.00 (s, 3H); HRMS (FAB) m/z 565.2222 [$(M + H)^+$ calcd for $C_{28}H_{33}N_6O_5S$ 565.2233]. Anal. ($C_{28}H_{32}N_6O_5S \cdot CF_3COOH$) C, H, N, S, F.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(phenylaminocarbonylamino)propionic Acid Trifluoroacetate (24h). A solution of **41a** (105 mg, 195 μmol) and iPr_2NEt (69 μL, 374 μmol) in CH_2Cl_2 (5 mL) was treated with phenyl isocyanate (60 μL, 552 μmol). After 60 min, the mixture was concentrated and purified by flash chromatography (hexanes:EtOAc 50:50) to provide **42a** (R = phenylaminocarbonyl) (72 mg, 56%): ^{1}H NMR ($CDCl_3$) δ 8.25 (d, J = 4.8 Hz, 1H), 8.19 (s, 1H), 7.97 (m, 1H), 7.86 (s, 1H), 7.74 (m, 2H), 7.58 (m, 2H), 7.17 (m, 2H), 7.13 (m, 2H), 6.94 (m, 2H), 6.63 (m, 1H), 4.79 (m, 1H), 4.35 (t, J = 7.0 Hz, 2H), 3.96 (t, J = 7.0 Hz, 2H), 3.80 (m, 2H), 2.25 (m, 2H), 1.46 (s, 9H), 1.40 (s, 9H); MS (FAB) m/z 658.5 [$(M + H)^+$, 100%]. This material was treated with TFA (0.8 mL) in CH_2Cl_2 (4 mL) for 3 h, concentrated, and purified by HPLC to provide **24h** (44 mg, 68%) as an amorphous white solid: ^{1}H NMR (MeOH-d_4) δ 8.24 (s, 1H), 8.09 (s, 1H), 7.78 (m, 2H), 7.68 (d, J = 6.2 Hz, 1H), 7.54 (d, J = 8.8 Hz, 1H), 7.30 (d, J = 8.4 Hz, 2H), 7.17 (t, J = 7.8 Hz, 2H), 6.91 (m, 2H), 6.80 (t, J = 6.2 Hz, 1H), 4.65 (m, 1H), 4.54 (t, J = 6.2 Hz, 2H), 3.80 (m, 2H), 3.31 (m, 2H), 2.30 (m, 2H); HRMS (FAB) m/z 502.2196 [$(M + H)^+$ calcd for $C_{26}H_{28}N_7O_4$ 502.2202]. Anal. ($C_{26}H_{27}N_7O_4 \cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(phenylmethylaminocarbonylamino)-propionic Acid Trifluoroacetate (24i). This compound was prepared as described for **24h** from **41a** and benzyl isocyanate as an amorphous white solid: ^{1}H NMR (MeOH-d_4) δ 8.24 (s, 1H), 8.13 (s, 1H), 7.80 (m, 2H), 7.67 (m, 1H), 7.57 (d, J = 9.1 Hz, 1H), 7.15 (m, 1H), 6.70 (m, 3H), 4.86 (m, 1H), 4.57 (t, J = 6.6 Hz, 2H), 4.27 (m, 2H), 3.62 (m, 2H), 3.28 (m, 2H), 3.27 (m, 2H); HRMS (FAB) m/z 516.2365 [$(M + H)^+$ calcd for $C_{27}H_{30}N_7O_4$ 516.2359]. Anal. ($C_{27}H_{29}N_7O_4 \cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(3-phenylpropionylamino)propionic Acid Trifluoroacetate (24j). A mixture of **41a** (100 mg, 186 μmol), hydrocinnamic acid (28 mg, 186 μmol), DCC (39 mg, 186 μmol), HOBT (25 mg, 186 μmol), and THF (5 mL) was stirred overnight and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc 60:40) to provide **42a** (R = hydrocinnamoyl) as a sticky solid, which was stirred with TFA (1 mL) in CH_2Cl_2 (3 mL) for 4 h, concentrated, and triturated with ether to provide **24j** (104 mg, 89%) as an amorphous white solid: ^{1}H NMR (DMSO-d_6) δ 8.56 (m, 1H), 8.30 (s, 1H), 8.25 (m, 2H), 7.89−7.75 (m, 4H), 7.18 (m, 5H), 6.95 (d, J = 8.00 Hz, 1H), 6.80 (t, J = 6.2 Hz, 1H), 4.54 (t, J = 6.6 Hz, 2H), 4.50 (m, 2H), 3.62(m, 2H), 3.40 (m, 1H), 3.22 (br, 1H), 2.80 (t, J = 9.0 Hz, 2H), 2.40 (t, J = 9.0 Hz, 1H), 2.20 (m, 2H); HRMS (FAB) m/z 515.2403 [$(M + H)^+$ calcd for $C_{28}H_{31}N_6O_4$ 515.2406]. Anal. ($C_{28}H_{30}N_6O_6 \cdot 1.2CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(4-methylpentanoylamino)propionic Acid Trifluoroacetate (24k). This compound was prepared as described for **24j** from **41a** and 4-methylvaleric acid as an amorphous white solid: ^{1}H NMR (MeOH-d_4) δ 8.55 (m, 2H), 8.29 (s, 1H), 8.24 (s, 1H), 8.14 (m, 1H), 7.80 (m, 2H), 6.96 (m, 1H), 6.80 (m, 1H), 4.70 (m, 1H), 4.60 (t, J = 7.0 Hz, 2H), 4.45 (m, 2H), 3.60 (m, 2H), 3.30 (m, 2H), 3.06 (m, 1H), 2.15 (m, 4H), 0.80 (d, J = 6.6 Hz, 6H); HRMS (FAB) m/z 481.2559 [$(M + H)^+$ calcd for $C_{25}H_{33}N_6O_4$ 481.2563]. Anal. ($C_{25}H_{32}N_6O_4 \cdot 1.4CF_3COOH \cdot 0.2H_2O$) C, H, N.

Using the procedure described for preparing **24g**, the following compounds were prepared from **41a**.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(benzenesulfonylamino)propionic acid trifluoroacetate (24m): from benzenesulfonyl chloride, as

an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.21 (s, 1H), 8.16 (s, 1H), 7.83 (m, 4H), 7.70 (d, J = 6.6 Hz, 1H), 7.57 (d, J = 8.7 Hz, 1H), 7.42 (m, 3H), 6.92 (d, J = 9.1 Hz, 1H), 6.83 (t, J = 6.6 Hz, 1H), 4.59 (t, J = 6.4 Hz, 2H), 4.23 (dd, J = 8.8, 4.8 Hz, 1H), 3.78 (dd, J = 13.6, 4.8 Hz, 1H), 3.49 (dd, J = 13.6, 8.8 Hz, 1H), 3.30 (m, 2H), 2.32 (m, 2H); HRMS (FAB) *m/z* 523.1763 [(M + H)$^+$ calcd for $C_{25}H_{27}N_6O_5S$ 523.1764]. Anal. ($C_{25}H_{27}N_6O_5S\cdot CF_3COOH$) C, H, N, S, F.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(1-butanesulfonylamino)propionic acid trifluoroacetate (24n): from 1-butanesulfonyl chloride, as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.28 (s, 1H), 8.15 (s, 1H), 7.8−7.1 (m, 3H), 6.87 (d, J = 9.1 Hz, 1H), 6.80 (d, J = 6.2 Hz, 1H), 4.58 (t, J = 6.2 Hz, 2H), 4.30(m, 1h), 3.86 (dd, J = 13.6, 4.8 Hz, 1H), 3.56 (dd, J = 13.5, 8.8 Hz, 1H), 3.26 (m, 2H), 3.03 (t, J = 8.0 Hz, 2H); HRMS (FAB) *m/z* 503.2076 [(M + H)$^+$ calcd for $C_{23}H_{29}N_6O_5S$ 503.2062]. Anal. ($C_{23}H_{28}N_6O_5S\cdot 1.1CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(phenylmethanesulfonylamino)propionic acid trifluoroacetate (24p): from phenylmethanesulfonyl chloride as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.25 (s, 1H), 8.13 (s, 1H), 7.67−7.8 (3H), 7.53 (d, J = 8.8 Hz, 1H), 7.40 (m, 2H), 7.30 (m, 3H), 6.82 (d, J = 9.2 Hz, 1H), 6.75 (t, J = 6.2 Hz, 1H), 4.56 (t, J = 6.6 Hz, 2H), 4.37 (s, 2H), 4.21 (m, 1H), 3.80 (dd, J = 13.6, 4.8 Hz, 1H), 3.57 (dd, J = 13.6, 8.4 Hz, 1H), 3.24 (t, J = 6.6 Hz, 2H), 2.29 (m, 2H); HRMS (FAB) *m/z* 537.1899 [(M + H) $^+$ calcd for $C_{26}H_{29}N_6O_5S$ 537.1920]. Anal. ($C_{26}H_{28}N_6O_5S\cdot 1.2CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(3-methylpropanesulfonylamino)propionic acid trifluoroacetate (24q): from 2-methylpropanesulfamyl chloride, as an amorphous white solid; ^{1}H NMR (DMSO-d_6) 8.72 (bs, 1H), 8.55 (m, 1H), 8.33 (s, 1H), 8.25 (s, 1H), 7.90 (m, 3H), 7.75 (d, J = 8.8 Hz, 1H), 7.22 (d, J = 8.8 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.92 (t, J = 5.9 Hz, 1H), 6.82 (t, J = 6.2 Hz, 1H), 4.58 (t, J = 6.2 Hz, 2H), 3.99 (m, 1H), 3.70 (m, 1H), 3.40 (m, 2H), 3.26 (m, 2H), 2.58 (m, 2H), 2.18 (m, 2H), 1.59 (m, 1H), 0.83 (t, J = 8.0 Hz, 6H); HRMS (FAB) *m/z* 518.2203 [(M + H)$^+$ calcd for $C_{23}H_{32}N_7O_5S$ 518.2185]. Anal. ($C_{23}H_{31}N_7O_5S\cdot 0.93CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(phenylmethylaminosulfonylamino)-propionic acid trifluoroacetate (24r): from phenylmethanesulfamyl chloride as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.56 (m, 2H), 8.33 (s, 1H), 8.24 (s, 1H), 7.90 (m, 3H), 7.74 (d, J = 8.8, 1H), 7.46 (m, 2H), 7.23 (m, 5H), 7.00 (t, J = 9.1 Hz, 1H), 4.56 (t, J = 6.6, 2H), 4.00 (m, 3H), 3.57 (m, 2H), 2.18 (m, 2H); HRMS (FAB) *m/z* 552.2042 [(M + H)$^+$ calcd for $C_{26}H_{30}N_7O_5S$ 552.2029]. Anal. ($C_{26}H_{29}N_7O_5S\cdot CF_3COOH\cdot H_2O$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(phenylaminosulfonylamino)propionic acid trifluoroacetate (24s): from benzenesulfamyl chloride as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.12 (s, 1H), 8.10 (s, 1H), 7.81 (m, 1H), 7.71 (m, 2H), 7.16−7.06 (m, 4H), 6.92 (d, J = 9.2 Hz, 1H), 6.82 (t, J = 6.3 Hz, 2H), 4.57 (t, J = 6.3 Hz, 2H), 4.25 (dd, J = 8.0, 4.7 Hz, 1H), 3.72 (dd, J = 13.6, 5.2 Hz, 1H), 3.52 (dd, J = 13.5, 8.4 Hz, 1H), 3.30 (m, 2H), 2.30 (m, 2H); HRMS (ESI) *m/z* 538.1887 [(M + H)$^+$ calcd for $C_{25}H_{28}N_7O_5S$ 538.1873]. Anal. ($C_{25}H_{27}N_7O_5S\cdot 1.1CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(2,4,6-trimethylphenylaminosulfonylamino)propionic acid trifluoroacetate (24t): from mesitylenesulfamyl chloride as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.24 (s, 1H), 8.13 (s, 1H), 7.78 (m, 2H), 7.66 (d, J = 5.9 Hz, 1H), 7.541 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 9.1 Hz, 1H), 6.80 (m, 3H), 4.56 (t, J = 6.6 Hz, 2H), 4.42 (m, 1H), 3.88 (dd, J = 13.9, 5.1 Hz, 1H), 3.68 (dd, J = 13.6, 7.7 Hz, 1H), 3.26 (t, J = 6.6 Hz, 2H), 2.34 (s, 6H), 2.29 (m, 2H), 2.17 (s, 3H); HRMS (FAB) *m/z* 580.2334 [(M + H)$^+$ calcd for $C_{28}H_{34}N_7O_5S$ 580.2342]. Anal. ($C_{28}H_{33}N_7O_5S\cdot CF_3COOH$) C, H, N.

***tert*-Butyl 3-[1-[3-(*N*-1-Triphenylmethylimidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-aminopropionate (41b).** Using the procedure described for **34a**, **33** and **6** were coupled to provide **40b** in 95% yield: ^{1}H NMR ($CDCl_3$) δ 8.11 (s, 1H), 7.93 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.40−7.15 (m, 20H), 7.04 (m, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.68 (d, J = 1.5 Hz, 1H), 6.41 (d, J = 1.5 Hz, 1H), 5.94 (bd, J = 6.6 Hz, 1H), 5.12 (s, 2H), 4.48 (m, 1H), 4.05 (t, J = 7.0 Hz, 2H), 3.85 (m, 2H), 3.10−2.90 (m, 3H), 1.80 (m, 2H), 1.47 (s, 9H); HRMS (FAB) *m/z* 804.3874 [(M + H)$^+$ calcd for $C_{48}H_{50}N_7O_5$ 804.3873]. Using the procedure described for **41a**, this material was converted to **41b** in 74% yield: ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.94 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.32 (m, 9H), 7.22 (m, 6H), 7.02 (d, J = 8.8 Hz, 1H), 6.93 (bt, J = 5.5, 1H), 6.68 (d, J = 1.8 Hz, 1H), 6.41 (d, J = 1.8 Hz, 1H), 4.06 (m, 2H), 3.85 (m, 1H), 3.63 (m, 1H), 3.51 (m, 1H), 3.05 (m, 1H), 2.97 (m, 2H), 1.83 (m, 4H), 1.49 (s, 9H); HRMS (FAB) *m/z* 670.3509 [(M + H)$^+$ calcd for $C_{40}H_{44}N_7O_3$ 670.3506]. Anal. ($C_{40}H_{43}N_7O_3\cdot 0.3H_2O$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(4-methylbenzenesulfonylamino)propionic Acid Trifluoroacetate (34h). Using the procedure described for the preparation of **24g**, **41b** was reacted with *p*-toluenesulfonyl chloride, and the intermediate was heated at reflux with TFA for 5 h; then the warm mixture was treated with water, cooled, concentrated, and purified by HPLC to provide **34h** (69% overall) as an amorphous white solid: ^{1}H NMR (MeOH-d_4) δ 8.19 (s, 1H), 8.15 (s, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.66 (d, J = 7.7 Hz, 2H), 7.56 (d, J = 8.8 Hz, 1H), 7.16 (d, J = 8.4 Hz, 2H), 4.56 (t, J = 6.2 Hz, 2H), 4.20 (m, 1H), 3.76 (dd, J = 13.5, 5.1 Hz, 1H), 3.47 (dd, J = 13.5, 8.8 Hz, 1H), 3.22 (t, J = 6.6 Hz, 2H), 2.24 (m, 2H), 2.18 (s, 3H); HRMS (FAB) *m/z* 526.1875 [(M + H) $^+$ calcd for $C_{24}H_{28}N_7O_5S$ 526.1873]. Anal. ($C_{24}H_{27}N_7O_5S\cdot CF_3COOH$) C, H, N.

Using the procedure described for preparing **34h**, the following compounds were prepared from **41b**.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(4-chlorobenzenesulfonylamino)propionic acid trifluoroacetate (34I): from 4-chlorobenzenesulfonyl chloride, as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.18 (s, 1H), 8.15 (s, 1H), 7.60 (m, 4H), 7.56 (d, J = 8.8 Hz, 1H), 7.55 (d, J = 8.7 Hz, 2H), 6.77 (s, 2H), 4.55 (t, J = 6.6 Hz, 2H), 4.26 (m, 1H), 3.78 (dd, J = 14.0, 5.2 Hz, 1H), 3.48 (dd, J = 13.6, 9.2 Hz, 1H), 3.23 (t, J = 6.6 Hz, 2H), 2.24 (m, 2H); HRMS (FAB) *m/z* 546.1320 [(M + H)$^+$ calcd for $C_{23}H_{25}ClN_7O_5S$ 546.1326]. Anal. ($C_{23}H_{24}ClN_7O_5S\cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(4-methoxybenzenesulfonylamino)-propionic acid trifluoroacetate (34j): from 4-methoxybenzenesulfonyl chloride, as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.16 (s, 1H), 8.13 (s, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 2H), 7.54 (d, J = 8.8 Hz, 1H), 6.81 (d, J = 8.8 Hz, 2H), 6.76 (s, 2H), 4.54 (t, J = 6.6 Hz, 2H), 4.20 (dd, J = 9.2, 5.1 Hz, 1H), 3.77 (dd, J = 13.6, 4.8 Hz, 1H), 3.62 (s, 3H), 3.48 (dd, J = 13.6, 8.8 Hz, 1H), 3.23 (t, J = 6.6 Hz, 2H), 2.22 (m, 2H); HRMS (FAB) *m/z* 568.2348 [(M + H)$^+$ calcd for $C_{24}H_{28}N_7O_6S$ 568.2342]. Anal. ($C_{24}H_{28}N_7O_6S\cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(4-trifluoromethylbenzenesulfonylamino)propionic acid trifluoroacetate (34k): from 4-trifluoromethylbenzenesulfonyl chloride, as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.20 (s, 1H), 8.13 (s, 1H), 7.98 (d, J = 8.4 Hz, 2H), 7.76 (m, 2H), 7.66 (m, 1H), 6.77 (s, 2H), 4.54 (t, J = 6.2 Hz, 2H), 4.32 (m, 1H), 3.80 (dd, J = 13.5, 4.7 Hz, 1H), 3.51 (dd, J = 13.5, 8.8 Hz, 1H), 3.23 (t, J = 6.6 Hz, 2H), 2.23 (m, 2H); HRMS (FAB) *m/z* 580.1605 [(M + H)$^+$ calcd for $C_{24}H_{25}F_3N_7O_5S$ 580.1590]. Anal. ($C_{24}H_{24}F_3N_7O_5S\cdot 0.9CF_3COOH\cdot 0.3CH_3CN$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(4-acetamidobenzenesulfonylamino)-propionic acid trifluoroacetate (34m): from 4-acetamidobenzenesulfonyl chloride, as an amorphous white solid; ^{1}H

NMR (MeOH-d_4) δ 8.11 (s, 1H), 8.10 (s, 1H), 7.72 (m, 3H), 7.51 (m, 3H), 6.76 (s, 2H), 4.53 (t, J = 6.2 Hz, 2H), 4.23 (m, 1H), 3.77 (dd, J = 13.6, 4.8 Hz, 1H), 3.47 (dd, J = 13.9, 8.0 Hz, 1H), 3.22 (t, J = 6.6 Hz, 2H), 2.22 (m, 2H), 2.02 (s, 3H); HRMS (FAB) m/z 569.1943 [(M + H)$^+$ calcd for $C_{25}H_{29}N_8O_6S$ 569.1931]. Anal. ($C_{25}H_{28}N_8O_6S\cdot CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(4-*tert*-butylbenzenesulfonylamino)-propionic acid trifluoroacetate (34n): from 4-*tert*-butylbenzenesulfonyl chloride, as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.25 (s, 1H), 8.17 (s, 1H), 7.82 (d, J = 10.6 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 6.78 (s, 2H), 4.56 (t, J = 6.6 Hz, 2H), 4.20 (m, 1H), 3.76 (dd, J = 13.5, 4.7 Hz, 1H), 3.50 (dd, J = 13.6, 8.8 Hz, 1H), 3.23 (t, J = 6.6 Hz, 2H), 2.24 (m, 2H), 1.20 (s, 9H); HRMS (FAB) m/z 568.2348 [(M + H)$^+$ calcd for $C_{27}H_{34}N_7O_5S$ 568.2342]. Anal. ($C_{27}H_{34}N_7O_5S\cdot 1.3CF_3COOH$) C, H, N.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(3,4-dichlorobenzenesulfonylamino)-propionic acid trifluoroacetate (34q): from 3,4-dichlorobenzenesulfonyl chloride, as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 8.15 (s, 1H), 8.13 (s, 1H), 7.86 (m, 1H), 7.66 (m, 2H), 7.50 (m, 1H), 7.40 (m, 2H), 6.77 (s, 2H), 4.32 (m, 1H), 3.80 (dd, J = 13.5, 4.7 Hz, 1H), 3.48 (dd, J = 13.6, 9.5 Hz, 1H), 3.23 (t, J = 6.6 Hz, 2H), 2.23 (m, 2H); HRMS (FAB) m/z 580.0940 [(M + H)$^+$ calcd for $C_{23}H_{24}Cl_2N_7O_5S$ 580.0937]. Anal. ($C_{23}H_{23}Cl_2N_7O_5S\cdot CF_3COOH$) C, H; N: calcd, 14.12; found, 13.50.

3-[1-[3-(*N*-Imidazol-2-ylamino)propyl]indazol-5-ylcarbonylamino]-2(*S*)-(2-naphthalenesulfonylamino)propionic acid trifluoroacetate (34v): from 2-naphthalenesulfonyl chloride as an amorphous white solid; ^{1}H NMR (MeOH-d_4) δ 7.99 (s, 1H), 7.97 (s, 1H), 7.73 (m, 3H), 7.56 (m, 2H), 7.35 (m, 3H), 6.75 (s, 2H), 4.47 (t, J = 6.2 Hz, 2H), 4.36 (m, 1H), 3.79 (dd, J = 13.5, 4.7 Hz, 1H), 3.48 (dd, J = 13.6, 9.6 Hz, 1H), 3.20 (t, J = 6.6 Hz, 2H), 2.20 (m, 2H); HRMS (FAB) m/z 562.1872 [(M + H)$^+$ calcd for $C_{27}H_{28}N_7O_5S$ 562.1873]. Anal. ($C_{27}H_{27}N_7O_5S\cdot 0.8CF_3COOH$) C, H, N.

1-(3-Oxopropyl)-5-nitroindazole (44). Using the procedures used to prepare **30** and **31**, 5-nitroindazole was converted into **44** in 23% overall yield as a pale yellow solid: ^{1}H NMR ($CDCl_3$) δ 9.85 (s, 1H), 8.71 (d, J = 2.2 Hz, 1H), 8.30 (dd, J = 9.2, 2.2 Hz, 1H), 8.21 (s, 1H), 7.62 (d, J = 9.2 Hz, 1H), 4.73 (t, J = 6.2 Hz, 2H), 3.24 (t, J = 6.2 Hz, 2H); HRMS (NH_3-CI) m/z 220.0732 [(M + H)$^+$ calcd for $C_{10}H_{10}N_3O_3$ 220.0722]. Anal. ($C_{10}H_9N_3O_3$) C, H, N.

1-(3-[*N*-Pyridin-2-ylamino]propyl)-5-nitroindazole (45). A solution of **44** (329 mg, 1.50 mmol) and 2-aminopyridine (282 mg, 3.0 mmol) in 1,2-dichloroethane (6 mL) was treated with $NaBH(OAc)_3$ (636 mg, 3.0 mmol) and stirred for 24 h. Aqueous $NaHCO_3$ was added, the mixture was extracted with CH_2Cl_2, and the extracts were dried and concentrated. The residue was purified by flash chromatography to provide **45** (414 mg, 92%) as a yellow solid: ^{1}H NMR ($CDCl_3$) δ 8.73 (d, J = 1.5 Hz, 1H), 8.24 (m, 2H), 8.16 (m, 1H), 7.45 (d, J = 9.2 Hz, 1H), 7.37 (m, 1H), 6.58 (m, 1H), 6.31 (d, J = 8.0 Hz, 1H), 4.61 (t, J = 6.5 Hz, 1H), 4.56 (t, J = 6.6 Hz, 2H), 3.32 (q, J = 6.2 Hz, 2H), 2.29 (m, 2H); HRMS (NH_3-CI) m/z 298.1289 [(M + H)$^+$ calcd for $C_{15}H_{16}N_5O_2$ 298.1304].

1-(3-[*N*-Pyridin-2-ylamino]propyl)-5-aminoindazole (46). A mixture of **45** (209 mg, 703 μmol), Fe powder (236 mg, 4.2 mmol), and HOAc (5 mL) was heated at 90 °C for 45 min, cooled, and poured cautiously into aqueous $NaHCO_3$. The mixture was stirred with EtOAc and filtered, and the solids were washed with EtOAc. The filtrate was extracted with EtOAc, and the extracts were dried and concentrated. The residue was purified by flash chromatography ($CHCl_3$: PrOH 92:8) to provide **46** (132 mg, 70%) as an off-white solid: ^{1}H NMR ($CDCl_3$) δ 8.06 (m, 1H), 7.80 (s, 1H), 7.37 (m, 1H), 7.25 (d, J = 8.8 Hz, 1H), 6.94 (d, J = 1.5 Hz, 1H), 6.85 (dd, J = 8.8, 1.5 Hz, 1H), 6.56 (m, 1H), 6.32 (d, J = 8.4 Hz, 1H), 4.74 (bt, J = 7.5 Hz, 1H), 4.44 (t, J = 6.6 Hz, 2H), 3.60 (bm, 2H), 3.26 (q, J = 6.6 Hz, 2H), 2.21 (m, 2H); HRMS (NH_3-CI) m/z 268.1576 [(M + H)$^+$ calcd for $C_{15}H_{18}N_5$ 268.1562].

***tert*-Butyl 3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylaminocarbonyl]-2(*S*)-(benzyloxycarbonylamino)-propionate (48).** A mixture of **46** (109 mg, 407 μmol), *N*-Cbz-aspartic acid 1-*tert*-butyl ester dicyclohexylamine salt (216 mg, 428 μmol), DCC (93 mg, 449 μmol), and HOBT (61 mg, 449 μmol) in DMF (3 mL) was stirred for 72 h and concentrated. The residue was purified by flash chromatography ($CHCl_3$: iPrOH 95:5) to give **48** (202 mg, 87%) as a white glassy foam: ^{1}H NMR ($CDCl_3$) δ 8.07 (m, 1H), 7.96 (m, 2H), 7.63 (bm, 1H), 7.4−7.3 (m, 8H), 6.56 (m, 1H), 6.32 (m, 1H), 6.00 (bm, 1H), 5.13 (s, 2H), 4.70 (bt, J = 7.0 Hz, 1H), 4.55 (m, 1H), 4.48 (t, J = 6.6 Hz, 2h), 3.25 (q, J = 6.6 Hz, 2H), 3.07 (m, 1H), 2.92 (m, 1H), 2.23 (m, 2H), 1.46 (s, 9H); HRMS (FAB) m/z 573.2843 [(M + H)$^+$ calcd for $C_{31}H_{37}N_6O_5$ 573.2825].

3-[1-[3-(*N*-Pyridin-2-ylamino)propyl]indazol-5-ylaminocarbonyl]-2(*S*)-(2,4,6-trimethylbenzenesulfonylamino)-propionic Acid Trifluoroacetate (49). Using the procedure described for the preparation of **24n**, **48** was converted into **49** as a white powder after ether trituration: ^{1}H NMR (MeOH-d_4) δ 7.98 (s, 1H), 7.91 (s, 1H), 7.82 (m, 1H), 7.72 (d, J = 6.6 Hz, 1H), 7.46 (d, J = 8.8 Hz, 1H), 7.32 (d, J = 8.8 Hz, 1H), 6.93 (d, J = 6.6 Hz, 1H), 6.88 (s, 2H), 6.83 (m, 1H), 4.54 (t, J = 6.4 Hz, 2H), 4.23 (dd, J = 7.2, 5.5 Hz, 1H), 3.28 (m, 2H), 2.83 (dd, J = 15.2, 5.3 Hz, 1H), 2.72 (dd, J = 15.2, 7.1 Hz, 1H), 2.61 (s, 6H), 2.29 (m, 2H), 2.15 (s, 3H); HRMS (FAB) m/z 565.2214 [(M + H)$^+$ calcd for $C_{28}H_{33}N_6O_5S$ 565.2233]. Anal. ($C_{28}H_{32}N_6O_5S\cdot 0.95CF_3COOH$) C, H, N, S, F.

***N*-Mesitylenesulfonyl-*N*′-*tert*-butyloxycarbonylethylenediamine (50).** A solution of *N*-Boc-ethylenediamine[47] (409 mg, 2.6 mmol) and Et_3N (395 μL, 2.8 mmol) in THF (15 mL) was treated at 0 °C with a solution of mesitylenesulfonyl chloride (614 mg, 2.8 mmol) in THF (4 mL) and warmed to room temperature. After 19 h, the mixture was diluted with water and extracted with CH_2Cl_2, and the extract was dried and concentrated. The residue was purified by flash chromatography (hexanes:EtOAc 75:25) to provide **50** (592 mg, 68%) as a white solid: mp 91−94 °C; ^{1}H NMR ($CDCl_3$) δ 6.96 (s, 2H), 5.22 (bs, 1H), 4.82 (bs, 1H), 3.22 (q, J = 5.5 Hz, 2H), 3.01 (q, J = 5.5 Hz, 2H), 2.63 (s, 6H), 2.30 (s, 3H), 1.43. (s, 9H); HRMS (NH_3-CI) m/z 343.1674 [(M + H)$^+$ calcd for $C_{16}H_{27}N_2O_4S$ 343.1692]. Anal. ($C_{16}H_{26}N_2O_4S$) C, H, N, S.

***N*-Mesitylenesulfonylethylenediamine Trifluoroacetate.** A solution of **50** (444 mg, 1.3 mmol) in CH_2Cl_2 (4 mL) and TFA (4 mL) was stirred for 3 h and concentrated, and the residue was triturated in ether to provide **51** (460 mg, 100%) as a white solid: ^{1}H NMR (DMSO-d_6) δ 7.81 (bs, 3H), 7.63 (t, J = 5.9 Hz, 1H), 7.07 (s, 2H), 2.91 (m, 2H), 2.84 (bm, 2H), 2.57 (s, 6H), 2.28 (s, 3H). Anal. ($C_{11}H_{18}N_2O_2S\cdot CF_3COOH$) C, H, N, S, F.

Adhesion of β_3-Transfected 293 Cells to Fibrinogen ($\alpha_v\beta_3$ 293β_3 assay). This assay has been described in detail.[22,42] Briefly, polystyrene EIA plates were coated with fibrinogen, blocked with bovine serum albumin in PBS, and washed. 293 human embryonic kidney cells expressing the human β_3 integrin subunit were preincubated for 15 min at 37 °C in either the presence or absence of test compound. The cell suspension was then added to the fibrinogen-coated plates and incubated for 60 min. The nonadherent cells were removed, the plates were washed with PBS, and the adherent cells were lysed. Aliquots were assayed for β-galactosidase activity, and IC_{50} values were determined by using standard curves and appropriate controls.

Aggregation of Gel-Purified Platelets (GPIIbIIIa GPP assay). Human platelet-rich plasma obtained from healthy volunteers was applied to a sepharose column to prepare gel-purified platelets as previously described.[48] Aliquots of gel-purified platelets (2×10^8 platelets/mL) along with 1 mM $CaCl_2$ and 1 mg/mL fibrinogen, with or without the test compounds at different concentrations, were assayed for aggregation as previously described for platelet-rich plasma,[48] and IC_{50} values were calculated.

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Supporting Information Available: 300-MHz ^{1}H NMR spectra and reverse-phase HPLC chromatograms of **34f**, **34q**, and **39.** This material is available free of charge via the Internet at http://pubs.acs.org.

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